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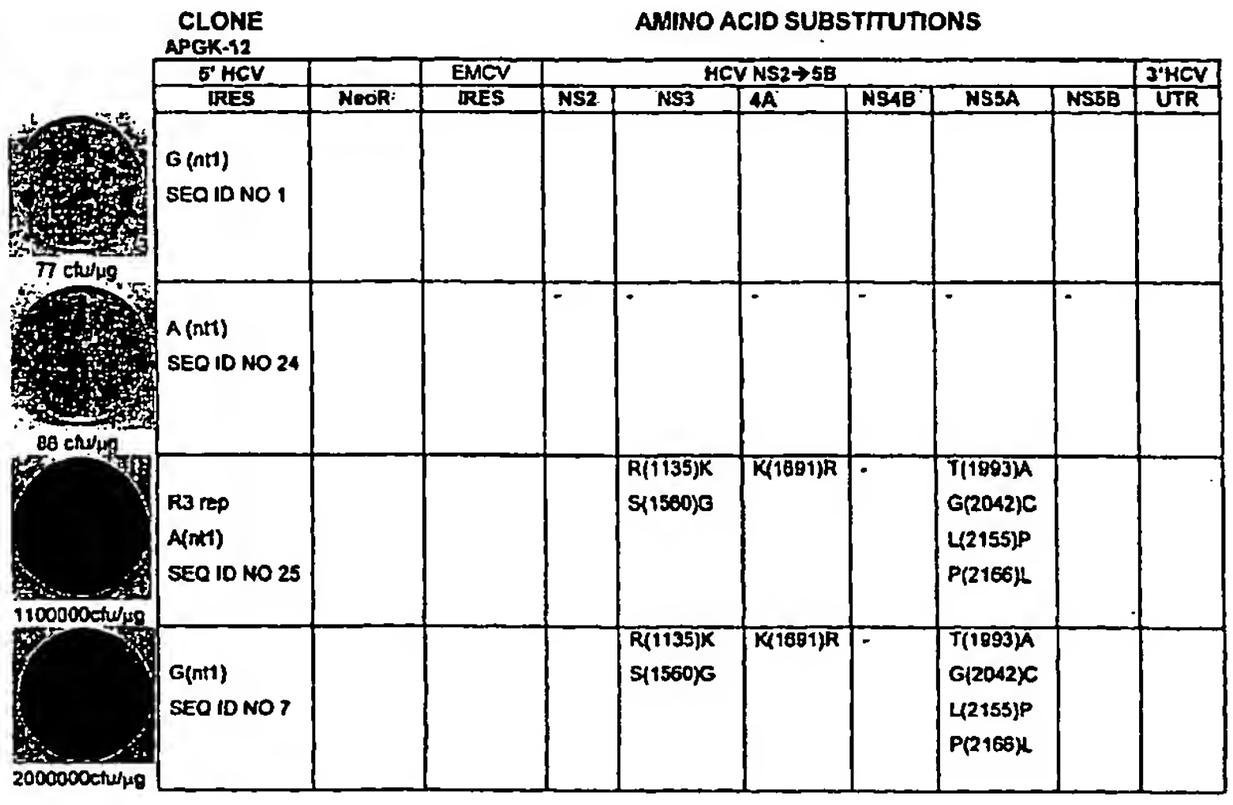

CLONE APGK-12 — AMINO ACID SUBSTITUTIONS

5' HCV IRES	NeoR	EMCV IRES	HCV NS2→5B NS2	NS3	4A	NS4B	NS5A	NS5B	3'HCV UTR
G (nt1) SEQ ID NO 1									
A (nt1) SEQ ID NO 24			-	-	-	-	-	-	
R3 rep A(nt1) SEQ ID NO 25				R(1135)K S(1560)G	K(1691)R	-	T(1993)A G(2042)C L(2155)P P(2166)L		
G(nt1) SEQ ID NO 7				R(1135)K S(1560)G	K(1691)R	-	T(1993)A G(2042)C L(2155)P P(2166)L		

(57) Abstract: A unique HCV RNA molecule is provided having an enhanced efficiency of establishing cell culture replication. Novel adaptive mutations have been identified within the HCV non-structural region that improves the efficiency of establishing persistently replicating HCV RNA in cell culture. This self-replicating polynucleotide molecule contains, contrary to all previous reports, a 5'-NTR that can be either an A as an alternative to the G already disclosed and therefore provides an alternative to existing systems comprising a self-replicating HCV RNA molecule. The G-->A mutation gives rise to HCV RNA molecules that, in conjunction with mutations in the HCV non-structural region, such as the G(2042)C/R mutations, possess greater efficiency of transduction and/or replication. These RNA molecules when transfected in a cell line are useful for evaluating potential inhibitors of HCV replication.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SELF-REPLICATING RNA MOLECULE FROM HEPATITIS C VIRUS

FIELD OF THE INVENTION

The present invention relates generally to a HCV RNA molecule that self-replicates in appropriate cell lines, particularly to a self-replicating HCV RNA construct having an enhanced efficiency of establishing cell culture replication.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is the major etiological agent of post-transfusion and community-acquired non-A non-B hepatitis worldwide. It is estimated that over 200 million people worldwide are infected by the virus. A high percentage of carriers become chronically infected and many progress to chronic liver disease, so called chronic hepatitis C. This group is in turn at high risk for serious liver disease such as liver cirrhosis, hepatocellular carcinoma and terminal liver disease leading to death. The mechanism by which HCV establishes viral persistence and causes a high rate of chronic liver disease has not been thoroughly elucidated. It is not known how HCV interacts with and evades the host immune system. In addition, the roles of cellular and humoral immune responses in protection against HCV infection and disease have yet to be established.

Various clinical studies have been conducted with the goal of identifying pharmaceutical compounds capable of effectively treating HCV infection in patients afflicted with chronic hepatitis C. These studies have involved the use of interferon-alpha, alone and in combination with other antiviral agents such as ribavirin. Such studies have shown that a substantial number of the participants do not respond to these therapies, and of those that do respond favorably, a large proportion were found to relapse after termination of treatment. To date there are no broadly effective antiviral compounds for treatment of HCV infection.

HCV is an enveloped positive strand RNA virus in the *Flaviviridae* family. The single strand HCV RNA genome is of positive polarity and comprises one open reading frame (ORF) of approximately 9600 nucleotides in length, which encodes a linear polyprotein of approx. 3010 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce structural and non-structural (NS) proteins. The structural proteins (C, E1, E2 and E2-p7) comprise

polypeptides that constitute the virus particle (Hijikata *et al.*, **1991**; Grakoui *et al.*, **1993(a)**). The non-structural proteins (NS2; NS3, NS4A, NS4B, NS5A, NS5B) encode for enzymes or accessory factors that catalyze and regulate the replication of the HCV RNA genome. Processing of the structural proteins is catalyzed by host cell proteases (Hijikata *et al.*, **1991**). The generation of the mature non-structural proteins is catalyzed by two virally encoded proteases. The first is the NS2/3 zinc-dependent metalloprotease which auto-catalyses the release of the NS3 protein from the polyprotein. The released NS3 contains a N-terminal serine protease domain (Grakoui *et al.*, **1993(b)**; Hijikata *et al.*, **1993**) and catalyzes the remaining cleavages from the polyprotein. The released NS4A protein has at least two roles. First, forming a stable complex with NS3 protein and assisting in the membrane localization of the NS3/NS4A complex (Kim *et al.*, Arch Virol. **1999,** 144: 329-343) and second, acting as a cofactor for NS3 protease activity. This membrane-associated complex, in turn catalyzes the cleavage of the remaining sites on the polyprotein, thus effecting the release of NS4B, NS5A and NS5B (Bartenschlager *et al.*, **1993**; Grakoui *et al.*, 1993(a); Hijikata *et al.*, **1993**; Love *et al.*, **1996**; reviewed in Kwong *et al.*, **1998**). The C-terminal segment of the NS3 protein also harbors nucleoside triphosphatase and RNA helicase activity (Kim *et al.*, **1995**). The function of the protein NS4B is unknown. NS5A, a highly phosphorylated protein, seems to be responsible for the Interferon resistance of various HCV genotypes (Gale Jr. *et al.* **1997** Virology 230, 217; Reed *et al.*, **1997**. NS5B is an RNA-dependent RNA polymerase (RdRp) that is involved in the replication of HCV.

The open reading frame of the HCV RNA genome is flanked on its 5' end by a non-translated region (NTR) of approx. 340 nucleotides that functions as the internal ribosome entry site (IRES), and on its 3' end by a NTR of approximately 230 nucleotides. Both the 5' and 3' NTRs are important for RNA genome replication. The genomic sequence variance is not evenly distributed over the genome and the 5'NTR and parts of the 3'NTR are the most highly conserved portions. The authentic, highly conserved 3'NTR is the object of US patent 5,874,565 granted to Rice *et al.*

The cloned and characterized partial and complete sequences of the HCV genome have also been analyzed with regard to appropriate targets for a prospective antiviral therapy. Four viral enzyme activities provide possible targets such as (1) the NS2/3 protease; (2) the NS3/4A protease complex, (3) the NS3 Helicase and (4) the NS5B

RNA-dependent RNA polymerase. The NS3/4A protease complex and the NS3 helicase have already been crystallized and their three-dimensional structure determined (Kim *et al.*, **1996**; Yem *et al.*, **1998**; Love *et al.*, **1996**; Kim *et al.*, **1998**; Yao *et al.*, **1997**; Cho *et al.*, **1998**). The NS5B RNA dependent RNA polymerase has also been crystallized to reveal a structure reminiscent of other nucleic acid polymerases (Bressanelli *et al.* **1999**, Proc. Natl. Acad. Sci, USA 96: 13034-13039; Ago *et al.* **1999**, Structure 7: 1417-1426; Lesburg *et al.* **1999**, Nat. Struct. Biol. 6: 937-943).

Even though important targets for the development of a therapy for chronic HCV infection have been defined with these enzymes and even though a worldwide intensive search for suitable inhibitors is ongoing with the aid of rational drug design and HTS, the development of therapy has one major deficiency, namely the lack of cell culture systems or simple animal models, which allow direct and reliable propagation of HCV viruses. The lack of an efficient cell culture system is still the main reason to date that an understanding of HCV replication remains elusive.

Although flavi- and pestivirus self-replicating RNAs have been described and used for the replication in different cell lines with a relatively high yield, similar experiments with HCV have not been successful to date (Khromykh *et al.*, **1997**; Behrens *et al.*, **1998**; Moser *et al.*, **1998**). It is known from different publications that cell lines or primary cell cultures can be infected with high-titer patient serum containing HCV (Lanford *et al.* **1994**; Shimizu *et al.* **1993**; Mizutani *et al.* **1996**; Ikda *et al.* **1998**; Fourner *et al.* **1998**; Ito *et al.* **1996**). However, these virus-infected cell lines or cell cultures do not allow the direct detection of HCV-RNA or HCV antigens.

It is also known from the publications of Yoo *et al.* **1995**; and of Dash *et al.*, **1997**; that hepatoma cell lines can be transfected with synthetic HCV-RNA obtained through *in vitro* transcription of the cloned HCV genome. In both publications the authors started from the basic idea that the viral HCV genome is a plus-strand RNA functioning directly as mRNA after being transfected into the cell, permitting the synthesis of viral proteins in the course of the translation process, and so new HCV particles could form HCV viruses and their RNA detected through RT-PCR. However the published results of the RT-PCR experiments indicate that the HCV replication in the described HCV transfected hepatoma cells is not particularly

efficient and not sufficient to measure the quality of replication, let alone measure the modulations in replication after exposure to potential antiviral drugs. Furthermore it is now known that the highly conserved 3' NTR is essential for the virus replication (Yanagi *et al.*, **1999**). This knowledge strictly contradicts the statements of Yoo *et al.* (*supra*) and Dash *et al.* (*supra*), who used for their experiments only HCV genomes with shorter 3' NTRs and not the authentic 3' end of the HCV genome.

In WO 98/39031, Rice *et al.* disclosed authentic HCV genome RNA sequences, in particular containing: a) the highly conserved 5'-terminal sequence "GCCAGCC"; b) the HCV polyprotein coding region; and c) 3'-NTR authentic sequences.

In WO 99/04008, Purcell *et al.* disclosed an HCV infectious clone that also contained only the highly conserved 5'-terminal sequence "GCCAGC".

Recently Lohman *et al.* **1999** (Science 285: 110-113) and Bartenschlager *et al.* (in CA 2,303,526, laid-open on October 3, 2000) disclosed a HCV cell culture system where the viral RNA (I377/NS2-3') self-replicates in the transfected cells with such efficiency that the quality of replication can be measured with accuracy and reproducibility. The Lohman and Bartenschlager disclosures were the first demonstration of HCV RNA replication in cell culture that was substantiated through direct measurement by Northern blots. This replicon system and sequences disclosed therein highlight once again the conserved 5' sequence "GCCAGC". A similar observation highlighting the conservation of the 5'NTR was made by Blight *et al.* **2000** (Science 290: 1972-1974) and WO 01/89364 published on Nov. 29, 2001.

In addition to the conservation of the 5' and 3' untranslated regions in cell culture replicating RNAs, three other publications by Lohman *et al.* **2001**, Krieger *et al.* **2001** and Guo *et al.* **2001** have recently disclosed distinct adaptive mutants within the HCV non-structural protein coding region. Specific nucleotide changes that alter the amino acids of the HCV non-structural proteins are shown to enhance the efficiency of establishing stable replicating HCV subgenomic replicons in culture cells.

Applicant has now found that, contrary to all previous reports, the highly conserved 5'-NTR can be mutated by adaptation to give rise to a HCV RNA sequence that, in conjunction with mutations in the HCV non-structural region, provides for a greater

efficiency of transduction and/or replication.

Applicant has also identified novel adaptive mutations within the HCV non-structural region that improves the efficiency of establishing persistently replicating HCV RNA in cell culture.

One advantage of the present invention is to provide an alternative to these existing systems comprising a HCV RNA molecule that self-replicates. Moreover, the present invention demonstrates that the initiating nucleotide of the plus-strand genome can be either an A as an alternative to the G already disclosed.

A further advantage of the present invention is to provide a unique HCV RNA molecule that transduces and/or replicates with higher efficiency. The Applicant demonstrates the utility of this specific RNA molecule in a cell line and its use in evaluating a specific inhibitor of HCV replication.

SUMMARY OF THE INVENTION

In a first embodiment, the present invention provides a 5'-non translated region of the hepatitis C virus wherein its highly conserved guanine at position 1 is substituted for adenine.

Particularly, the present invention provides a hepatitis C virus polynucleotide comprising adenine at position 1 as numbered according to the I377/NS2-3' construct (Lohmann et al. 1999, Accession # AJ242651).

Particularly, the invention provides a HCV self-replicating polynucleotide comprising a 5'-terminus consisting of ACCAGC (**SEQ ID NO. 8**).

In a second embodiment, the present invention is directed to a HCV self-replicating polynucleotide encoding a polyprotein comprising one or more amino acid substitution selected from the group consisting of: R(1135)K; S(1148)G; S(1560)G; K(1691)R; L(1701)F; I(1984)V; T(1993)A; G(2042)C; G(2042)R; S(2404)P; L(2155)P; P(2166)L and M(2992)T.

Particularly, the invention is directed to a HCV self-replicating polynucleotide encoding a polyprotein comprising the any one of the amino acid substitutions as described above, further comprising the amino acid substitution E(1202)G.

More particularly, the invention provides a HCV self-replicating polynucleotide encoding a polyprotein comprising a G2042C or a G2042R mutation.

Most particularly, the invention provides for HCV self-replicating polynucleotide comprising a nucleotide substitution G-->A at position 1, and said polynucleotide encodes a polyprotein further comprising a G2042C or a G2042R mutation.

Particularly, the polynucleotide of the present invention can be in the form of RNA or DNA that can be transcribed to RNA.

In a third embodiment, the invention also provides for an expression vector comprising a DNA form of the above polynucleotide, operably linked with a promoter.

According to a fourth embodiment, there is provided a host cell transfected with the self-replicating polynucleotide or the vector as described above.

In a fifth embodiment, the present invention provides a RNA replication assay comprising the steps of:

- incubating the host cell as described above in the absence or presence of a potential hepatitis C virus inhibitor;
- isolating the total cellular RNA from the cells;
- analyzing the RNA so as to measure the amount of HCV RNA replicated;
- comparing the levels of HCV RNA in cells in the absence and presence of the inhibitor.

In a sixth embodiment, the invention is directed to a method for testing a compound for inhibiting HCV replication, including the steps of:

a) treating the above described host cell with the compound;

b) evaluating the treated host cell for reduced replication, wherein reduced replication indicates the ability of the compound to inhibit replication.

DETAILED DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic view of the bi-cistronic replicon RNA. The sequence deviations between the I377/NS2-3' replicon from Lohman *et al.*, 1999 and the APGK12 replicon are indicated below the replicon. In place of a G nucleotide at the +1 position in the I377/NS2-3'replicon, the APGK12 contains an additional G resulting in GG at the 5' terminus (the first G being counted as position –1). In the linker region between the neo gene and the EMCV IRES sequence two areas deviate from I377/NS2-3': 14 nucleotides (CGCGCCCAGATGTT) which are not present in I377/NS2/3 are inserted at position 1184 in APGK12; 11 nucleotides (1231-1241) present in I377/NS2-3' are deleted to generate APGK-12. In the NS5B coding region, a T at position 8032 was mutated to C to eliminate a NcoI restriction site.

Figure 2 shows Northern blots of RNA-transfected Huh-7 cell lines. 12 µg of total cellular RNA or control RNA was separated on 0.5% agarose–formaldehyde gels and transferred to Hybond N+ paper, fixed and (Figure 2A) radioactively probed with HCV specific minus-strand RNA that detects the presence of plus-strand replicon RNA. Lanes 1 and 2: positive controls that contain 10^9 copies *of in vitro* transcribed APGK12 RNA. Lane 3: negative control of total cellular RNA from untransfected Huh-7 cells. Lanes 4 and 5: cellular RNA from B1 and B3 cell lines that have integrated DNA copies of the neomycin phosphotransferase gene. Lane 6: total cellular RNA from a Huh-7 cell line, designated S22.3, that harbors high copy number HCV sub-genomic replicon RNA as highlighted by the arrow. Other cell lines have no detectable replicon RNA. Figure 2B is identical to Figure 2A with the exception that the blot was radioactively probed with HCV specific plus-strand RNA to detect the presence of HCV minus-strand RNA. Lanes 1 and 2 are positive control lanes that contain 10^9 copies of full length HCV minus strand RNA. Lane 6, which contains 12 µg of total cellular RNA from cell line S22.3, harbors detectable minus-strand replicon RNA at the expected size of 8 – 9 kilobases. M represent the migration of non-radioactive molecular size markers on the agarose gel. 28s represents the migration of 28s ribosomal RNA and accounts for the detection of this species in a samples of total cellular RNA.

Figure 3 shows indirect immunofluorescence of a HCV non-structural protein in the

S22.3 cell line. Indirect immunofluorescence was performed on cells that were cultured and fixed, permeabilized and exposed to a rabbit polyclonal antibody specific for a segment of the HCV NS4A protein. Secondary goat anti-rabbit antibody conjugated with red-fluor Alexa 594 (Molecular Probes) was used for detection. Top panels shows the results of immunofluorescence (40X objective) and the specific staining of the S22.3 cells. The bottom panels represent the identical field of cells viewed by diffractive interference contrast (DIC) microscopy. The majority of S22.3 (Figure 3A) cells within the field stain positively for HCV NS4A protein that localizes in the cytoplasm, whereas the B1 cells (Figure 3B) that fail to express any HCV proteins, only have background level of staining.

Figure 4 shows Western-blots following SDS-PAGE separation of total proteins extracted from three cell lines: (i) naïve Huh-7 cell line, (ii) neomycin resistant Huh-7 cell line B1, and (iii) the S22.3 cell line. Panels A, B, and C, demonstrate the results of western blots probed with rabbit polyclonal antisera specific for neomycin phosphotransferase (NPT), HCV NS3, and HCV NS5B, respectively. Visualization was achieved through autoradiographic detection of a chemiluminescent reactive secondary \ goat anti-rabbit antibody. Panel A shows that the S22.3 RNA replicon cell line, expresses the NPT protein at levels higher than control B1 cells and that the naïve Huh-7 cell line does not produce the NPT protein. Panels B and C show that only the S22.3 cell line produces the mature HCV NS3 and NS5B proteins, respectively. M represents molecular weight (in kilodaltons) of pre-stained polypeptide markers.

Figure 5A and 5B identify the nucleotide and amino acid sequences respectively that differ from the APGK12 sequence in the different HCV bi-cistronic replicons. The S22.3 adapted replicon is a first generation replicon selected following the transfection of RNA transcribed from the APGK12 template. R3, R7, R16 are second generation replicons that were selected following the transfection of RNA isolated from the S22.3 first generation replicon cell line. Figure 5A: Nucleotide mutations that were characterized in each of the adapted replicons are indicated adjacent to the respective segment of the replicon (IRES, NS3, NS4A, NS5A, and NS5B). Figure 5B: Amino acid numbers are numbered according to the full length HCV poly-protein with the first amino acid in the second cistron corresponding to amino acid 810 in NS2 of I377/NS2-3' construct.

Figure 6 depicts the colony formation efficiency of four *in vitro* transcribed HCV sub-genomic bi-cistronic replicon RNAs. The APGK12 serves as the reference sequence; highlighted are the initiating nucleotides of the HCV IRES in each of the constructs and the amino acid differences (from the APGK12 reference sequence) in the HCV non-structural region for the two R3-rep. Note that the *in vitro* transcribed APGK-12 RNAs that harbor either a 5'G or 5'A form colonies with the same efficiency (ca. 80 cfu/µg in panels A and B) following selection with 0.25 mg/ml G418. RNA isolated from the second generation R3 cell line was reverse transcribed into DNA and cloned into the pAPGK12 vector backbone to generate the R3-rep, which was sequenced and found to encode additional changes that included the L(2155)P substitution in the NS5A segment of the HCV polyprotein (compare R3-rep sequence with the R3 sequence in tables 2 and 3). Various quantities of in vitro transcribed R3-rep-5'A RNA, were transfected into naïve Huh-7 cells to determine a colony formation efficiency of 1.2 X 10^6 cfu/µg of RNA (panel C). Various quantities of R3-rep-5'G were also transfected resulting in a colony formation efficiency of 2 X 10^6 cfu/µg of RNA (panel D).

Figure 7 displays a typical RT-PCR amplification plot (left panel) and the graphical representation of Ct values versus known HCV RNA quantity in a standard curve (right panel). Each of the plotted curves in the left panel, graph the increment of fluorescence reporter signal (delta-Rn) versus PCR cycle number for a predetermined quantity of HCV replicon RNA. The Ct value is obtained by determining the point at which the fluorescence exceeds an arbitrary value (horizontal line). The right panel demonstrates the linear relationship between starting RNA copy number of the predetermined standards (large black dots) and the Ct value. Smaller dots are the Ct values of RNA samples (containing unknown quantity of HCV replicon RNA) from S22.3 cells treated with various concentrations of a specific inhibitor of HCV replication.

Figure 8 shows the effect of increasing concentration of inhibitor A on HCV RNA replicon levels in Huh7 cells. S22.3 cells were grown in the presence of increasing concentrations of inhibitor A starting at 0.5nM and ranging to 1024nM. The inhibitor dose-response curve is the result of 11 concentrations from serial two-fold dilutions (1:1). One control well, without any inhibitor, was also included during the course of

the experiment. The cells were incubated for 4 days in a 5% CO_2 incubator at 37 °C. Total cellular RNA was extracted, quantified by optical density. HCV replicon RNA was evaluated by real time RT-PCR and plotted as genome equivalents/µg total RNA as a function of inhibitor concentration

Definitions

Unless defined otherwise, the scientific and technological terms and nomenclature used herein have the same meaning as commonly understood by a person of ordinary skill to which this invention pertains. Generally, the procedures for cell culture, infection, molecular biology methods and the like are common methods used in the art. Such standard techniques can be found in reference manuals such as for example Sambrook *et al.* (1989) and Ausubel *et al.* (1994).

Nucleotide sequences are presented herein by single strand, in the 5' to 3' direction, from left to right, using the one letter nucleotide symbols as commonly used in the art and in accordance with the recommendations of the IUPAC-IUB Biochemical Nomenclature Commission (1972).

The present description refers to a number of routinely used recombinant DNA (rDNA) technology terms. Nevertheless, definitions of selected examples of such rDNA terms are provided for clarity and consistency.

The term "DNA segment or molecule or sequence", is used herein, to refer to molecules comprised of the deoxyribonucleotides adenine (A), guanine (G), thymine (T) and/or cytosine (C). These segments, molecules or sequences can be found in nature or synthetically derived. When read in accordance with the genetic code, these sequences can encode a linear stretch or sequence of amino acids which can be referred to as a polypeptide, protein, protein fragment and the like.

As used herein, the term "gene" is well known in the art and relates to a nucleic acid sequence defining a single protein or polypeptide. The polypeptide can be encoded by a full-length sequence or any portion of the coding sequence, so long as the functional activity of the protein is retained.

A "structural gene" defines a DNA sequence which is transcribed into RNA and translated into a protein having a specific structural function that constitute the viral particles. "Structural proteins" defines the HCV proteins incorporated into the virus particles namely, core "C", E1, E2, and E2-p7.

"Non-structural proteins", defines the HCV proteins that are not comprised in viral particles namely, NS2, NS3, NS4A, NS5A and NS5B.

"Restriction endonuclease or restriction enzyme" is an enzyme that has the capacity to recognize a specific base sequence (usually 4, 5 or 6 base pairs in length) in a DNA molecule, and to cleave the DNA molecule at every place where this sequence appears. An example of such an enzyme is *EcoRI*, which recognizes the base sequence G↓AATTC and cleaves a DNA molecule at this recognition site.

"Restriction fragments" are DNA molecules produced by the digestion of DNA with a restriction endonuclease. Any given genome or DNA segment can be digested by a particular restriction endonuclease into at least two discrete molecules of restriction fragments.

"Agarose gel electrophoresis" is an analytical method for fractionating polynucleotide molecules based on their size. The method is based on the fact that nucleic acid molecules migrate through a gel as through a sieve, whereby the smallest molecule has the greatest mobility and travels the farthest through the gel. The sieving characteristics of the gel retards the largest molecules such that, these have the least mobility. The fractionated polynucleotides can be visualized by staining the gel using methods well known in the art, nucleic acid hybridization or by tagging the fractionated molecules with a detectable label. All these methods are well known in the art, specific methods can be found in Ausubel *et al. (supra).*

"Oligonucleotide or oligomer" is a molecule comprised of two or more deoxyribonucleotides or ribonucleotides, preferably more than three. The exact size of the molecule will depend on many factors, which in turn depend on the ultimate function or use of the oligonucleotide . An oligonucleotide can be derived synthetically, by cloning or by amplification.

"Sequence amplification" is a method for generating large amounts of a target sequence. In general, one or more amplification primers are annealed to a nucleic acid sequence. Using appropriate enzymes, sequences found adjacent to, or in between the primers are amplified. An amplification method used herein is the polymerase chain reaction (PCR) and can be used in conjunction with the reverse-transcriptase (RT) to produce amplified DNA copies of specific RNA sequences.

"Amplification primer" refers to an oligonucleotide, capable of annealing to a RNA or DNA region adjacent to a target sequence and serving as the initiation primer for DNA synthesis under suitable conditions well known in the art. The synthesized primer extension product is complementary to the target sequence.

The term "domain" or "region" refers to a specific amino acid sequence that defines either a specific function or structure within a protein. As an example herein, is the

NS3 protease domain comprised within the HCV non-structural polyprotein.

The terms "plasmid" "vector" or "DNA construct" are commonly known in the art and refer to any genetic element, including, but not limited to, plasmid DNA, phage DNA, viral DNA and the like which can incorporate the oligonucleotide sequences, or sequences of the present invention and serve as DNA vehicle into which DNA of the present invention can be cloned. Numerous types of vectors exist and are well known in the art.

The terminology "expression vector" defines a vector as described above but designed to enable the expression of an inserted sequence following transformation or transfection into a host. The cloned gene (inserted sequence) is usually placed under the control of control element sequences such as promoter sequences. Such expression control sequences will vary depending on whether the vector is designed to express the operably linked gene *in vitro* or *in vivo* in a prokaryotic or eukaryotic host or both (shuttle vectors) and can additionally contain transcriptional elements such as enhancer elements, termination sequences, tissue-specificity elements, and/or translational initiation and termination sites.

A host cell or indicator cell has been "transfected" by exogenous or heterologous DNA (e.g. a DNA construct) or RNA, when such nucleic acid has been introduced inside the cell. The transfecting DNA may or may not be integrated (covalently linked) into chromosomal DNA making up the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transfecting/transforming DNA may be maintained on an episomal element such as a plasmid. With respect to eukaryotic cells, an example of a stably transfected cell is one in which the transfecting DNA has become integrated into a chromosome and is inherited by daughter cells through chromosome replication. A host cell or indicator cell can be transfected with RNA. A cell can be stably transfected with RNA if the RNA replicates and copies of the RNA segregate to daughter cells upon cell division. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transfecting DNA or RNA. Transfection methods are well known in the art (Sambrook *et al.*, 1989; Ausubel *et al.*, 1994). If the RNA encodes for a genetic marker that imparts an observable phenotype, such as antibiotic resistance, then the stable transfection of replicating RNA can be monitored by the acquisition of such phenotype by the host cell.

As used herein the term "transduction" refers to the transfer of a genetic marker to host cells by the stable transfection of a replicating RNA.

The nucleotide sequences and polypeptides useful to practice the invention include without being limited thereto, mutants, homologs, subtypes, quasi-species, alleles, and the like. It is understood that generally, the sequences of the present invention encode a polyprotein. It will be clear to a person skilled in the art that the polyprotein of the present invention and any variant, derivative or fragment thereof, is auto-processed to an active protease.

As used herein, the designation "variant " denotes in the context of this invention a sequence whether a nucleic acid or amino acid, a molecule that retains a biological activity (either functional or structural) that is substantially similar to that of the original sequence. This variant may be from the same or different species and may be a natural variant or be prepared synthetically. Such variants include amino acid sequences having substitutions, deletions, or additions of one or more amino acids, provided the biological activity of the protein is conserved. The same applies to variants of nucleic acid sequences which can have substitutions, deletions, or additions of one or more nucleotides, provided that the biological activity of the sequence is generally maintained.

The term "derivative" is intended to include any of the above described variants when comprising additional chemical moiety not normally a part of these molecules. These chemical moieties can have varying purposes including, improving a molecule's solubility, absorption, biological half life, decreasing toxicity and eliminating or decreasing undesirable side effects. Furthermore, these moieties can be used for the purpose of labeling, binding, or they may be comprised in fusion product(s). Different moieties capable of mediating the above described effects can be found in *Remington's The Science and Practice of Pharmacy* (1995). Methodologies for coupling such moieties to a molecule are well known in the art.

The term "fragment" refers to any segment of an identified DNA, RNA or amino acid sequence and/or any segment of any of the variants or derivatives described herein above that substantially retains its biological activity (functional or structural) as required by the present invention.

The terms "variant", "derivative", and "fragment" of the present invention refer herein to proteins or nucleic acid molecules which can be isolated/purified, synthesized chemically or produced through recombinant DNA technology. All these methods are well known in the art. As exemplified herein below, the nucleotide sequences and polypeptides used in the present invention can be modified, for example by *in vitro* mutagenesis.

As used herein, the term "HCV polyprotein coding region" means the portion of a hepatitis C virus that codes for the polyprotein open reading frame (ORF). This ORF may encode proteins that are the same or different than wild-type HCV proteins. The ORF may also encode only some of the functional protein encoded by wild-type polyprotein coding region. The protein encoded therein may also be from different isolates of HCV, and non-HCV protein may also be encoded therein.

As used herein, the abbreviation "NTR" used in the context of a polynucleotide molecule means a non-translated region. The term "UTR" means untranslated region. Both are used interchangeably.

Preferred embodiments

Particularly, the invention provides a HCV self-replicating polynucleotide molecule comprising a 5'-terminus consisting of ACCAGC (**SEQ ID NO.8**).

According to the first embodiment of this invention, there is particularly provided a HCV polynucleotide construct comprising:

- a 5'-non translated region (NTR) comprising the sequence ACCAGC at, or proximal to, its 5'-terminus;
- a HCV polyprotein coding region; and
- a 3'-NTR region.

In a second embodiment, the present invention is directed to a HCV self-replicating polynucleotide encoding a polyprotein comprising one or more amino acid substitution selected from the group consisting of: R(1135)K; S(1148)G; S(1560)G; K(1691)R; L(1701)F; I(1984)V; T(1993)A; G(2042)C; G(2042)R; S(2404)P; L(2155)P; P(2166)L and M(2992)T.

Particularly, the invention is directed to a HCV self-replicating polynucleotide encoding a polyprotein comprising the any one of the amino acid substitutions as described above, further comprising the amino acid substitution E(1202)G.

Alternatively, the first embodiment of the present invention is directed to HCV self-replicating polynucleotide molecule comprising a G2042C/R mutation.

According to the second embodiment, the present invention particularly provides a HCV polynucleotide construct comprising:

- a 5'-NTR region comprising the sequence ACCAGC at, or proximal to, its 5'-terminus;
- a HCV polyprotein region coding for a HCV polyprotein comprising a **G**(2042)**C** or a **G**(2042)**R** mutation; and
- a 3'-NTR region.

Preferably, the polynucleotide construct of the present invention is a DNA or RNA molecule. More preferably, the construct is a RNA molecule. Most preferably, the construct is a DNA molecule.

More particularly, the first embodiment of this invention is directed to a RNA molecule encoded by the DNA molecule selected from the group consisting of: SEQ ID NO. 2, 4, 5, 6, 7, 24 and 25.

Most particularly, the invention provides a DNA molecule selected from the group consisting of: SEQ ID NO. 2, 4, 5, 6, 7, 24 and 25.

In a third embodiment, the invention also is directed to an expression vector comprising DNA forms of the above polynucleotide, operably linked with a promoter.

Preferably, the promoter is selected from the group consisting of: T3, T7 and SP6.

According to a fourth embodiment, there is provided a host cell transfected with the self-replicating polynucleotide or vector as described above. Particularly, the host cell is a eukaryotic cell line. More particularly, the eukaryotic cell line is a hepatic cell line. Most particularly, the hepatic cell line is Huh-7.

In a fifth embodiment, the present invention provides a RNA replication assay comprising the steps of:

a) incubating the host cell as described above under conditions suitable for RNA replication;

b) isolating the total cellular RNA from the cells; and

c) analyzing the RNA so as to measure the amount of HCV RNA replicated.

Preferably, the analysis of RNA levels in step c) is carried out by amplifying the RNA by real-time RT-PCR analysis using HCV specific primers so as to measure the amount of HCV RNA replicated.

Alternatively in this fifth embodiment, the construct comprises a reporter gene, and the analysis of RNA levels in step c) is carried out by assessing the level of reporter expressed.

According to a preferred aspect of the sixth embodiment, the invention is directed to a method for testing a compound for inhibiting HCV replication, including the steps of:

a) carrying step a) as described in the above assay, in the presence or absence of the compound;

b) isolating the total cellular RNA from the cells; and

c) analyzing the RNA so as to measure the amount of HCV RNA replicated.

d) comparing the levels of HCV RNA in cells in the absence and presence of the inhibitor,

wherein reduced RNA levels is indicative of the ability of the compound to inhibit replication.

Preferably, the cell line is incubated with the test compound for about 3-4 days at a temperature of about 37°C.

EXAMPLES

EXAMPLE 1

Replicon Constructs (APGK-12; Figure 1)

pET9a-EMCV was obtained by ligating an oligonucleotide linker 5' gaattccagatggcgcgcccagatgttaaccagatccatggcacactctagagtactgtcgac 3' (**SEQ ID NO.9**) to pET-9a (Novagen) that was cut with EcoRI and SalI to form the vector pET-9a-mod. This linker contains the following restriction sites: EcoRI, AscI, HpaI, NcoI, XbaI, ScaI, SalI. The EMCV IRES was amplified by PCR from the vector pTM1 with primers

5' cggaatcgttaacagaccacaacggtttccctc 3' (**SEQ ID NO.10**) and 5' ggcgtacccatggtattatcgtgtttttca 3' (**SEQ ID NO.11**) and ligated into pET-9a-mod via EcoRI and NcoI to form pET-9a-EMCV.

The sequence of HCV NS2 to NS5B followed by the 3'UTR of HCV was obtained from the replicon construct I377/NS2-3' (Lohman *et al.*, 1999; accession number: AJ242651) and synthesized by Operon Technologies Inc. with a T to C change at the NcoI site in NS5B at nucleotide 8032. This sequence was released from an GenOp® vector (Operon Technologies) with NcoI and ScaI and transferred into pET-9a-EMCV to form pET-9a-EMCV-NS2-5B-3'UTR.

pET-9a-HCV-neo was obtained by amplification of the HCV IRES from a HCV cDNA isolated from patient serum with primers 5' gcatatgaattctaatacgactcactataggccagcccccgattg 3' (**SEQ ID NO.12**) containing a T7 promoter and primer 5' ggcgcgccctttggtttttctttgaggtttaggattcgtgctcat 3' (**SEQ ID NO.13**) and amplification of the neomycin phosphotransferase gene from the vector pcDNA 3.1 (Invitrogen) with primers 5' aaagggcgcatgattgaacaagatggattgcacgca 3' (**SEQ ID NO.14**) and 5' gcatatgttaactcagaagaactcgtcaagaaggcgata 3' (**SEQ ID NO.15**). These two PCR fragments were mixed and amplified with primers 5' gcatatgaattctaatacgactcactataggccagcccccgattg 3' (**SEQ ID NO.16**) and 5' gcatatgttaactcagaagaactcgtcaagaaggcgata 3' (**SEQ ID NO.15**), cut with Eco RI and HpaI and transferred into pET-9a-mod to form pet-9a-HCV-neo. The EMCV-NS2-5B-3'UTR was released from pET-9a-EMCV-NS2-5B-3'UTR with HpaI and ScaI and transferred into pet-9a-HCV-neo that was cut with HpaI to form pET-9a-APGK12. This insert was sequenced with specific successive primers using a ABI Prism® BigDye™ Terminator Cycle sequencing kit and analyzed on ABI Prism® 377 DNA Sequencer and is shown in **SEQ ID NO 1**.

RNA *in vitro* transcription

pET-9a-APGK12 DNA was cut with ScaI for expression of the full-length replicon or with BglII for expression of a truncated negative control RNA. DNA was analyzed on a 1% agarose gel and purified by Phenol/Chloroform extraction. RNA was produced using a T7 Ribomax® kit (Promega) followed by extraction with phenol/chloroform

and precipitation with 7.5 M $LiCl_2$. RNA was treated with DNAse I for 15 min to remove the DNA template and further purified with an RNeasy® column (Qiagen). RNA integrity was verified on a denaturing formaldehyde 1% agarose gel.

EXAMPLE 2

Primary transfection of Huh7 cells and selection of replicon cell lines

Human hepatoma Huh7 cells (Health Science Research Resources Bank, Osaka, Japan) were grown in 10% FBS/DMEM. Cells were grown to 70% confluency, trypsinized, washed with phosphate buffered saline (PBS) and adjusted to $1x10^7$ cells/ml of PBS. 800 µl of cells were transferred into 0.4cm cuvettes and mixed with 15 µg of replicon RNA. Cells were electroporated using 960µF, 300 volts for ~18 msec and evenly distributed into two 15 cm tissue culture plates and incubated in a tissue culture incubator for 24 hours. The selection of first and second generation replicon cell lines was with 10% FBS/DMEM medium supplemented with 1mg/ml of G418. Cells were selected for 3-5 weeks until colonies were observed that were isolated and expanded.

Following the G418 selection and propagation of Huh-7 cells transfected with APGK12 (**SEQ ID NO. 1**) RNA, cells that formed a distinct colony were treated with trypsin and serially passed into larger culture flasks to establish cell lines. Approximately 10 X 10^6 cells were harvested from each cell line. The cells were lysed and the total cellular RNA extracted and purified as outlined in Qiagen RNAeasy® preparatory procedures. Figure 2 shows the analysis of 12 µg of total cellular RNA from various cell lines as analyzed on a Northern blot of a denaturing agarose-formaldehyde gel.

Figure 2A is a Northern blot (radioactively probed with HCV specific minus-strand RNA) that detects the presence of plus-strand replicon RNA. Lanes 1 and 2 are positive controls that contain 10^9 copies *of in vitro* transcribed APGK12 RNA. Lane 2 contains the *in vitro* transcribed RNA mixed with 12 µg of total cellular from naïve Huh-7 cells. Lane 3 is a negative control of total cellular RNA from untreated Huh-7 cells. Lanes 4 and 5 contain cellular RNA from the B1 and B3 G418 resistant cell lines that have DNA integrated copies of the neomycin phosphotransferase gene. Lane 6 contains total cellular RNA from a Huh-7 cell line, designated S22.3, that

harbors high copy number of HCV sub-genomic replicon RNA as detected by the positive signal in the 8 kilo-base range. Other cell lines have no detectable replicon RNA. Figure 2B is a Northern blot of a duplicate of the gel presented in 2A with the exception that the blot was radioactively probed with HCV specific plus-strand RNA to detect the presence of HCV minus-strand RNA (lanes 1 and 2 are positive control lanes that contain 10^9 copies of full length genomic HCV minus strand RNA); only lane 6, which contains 12 μg of total cellular RNA from cell line S22.3, harbors detectable minus-strand replicon RNA at the expected size of 8 – 9 kilobases. An quantitative estimation of RNA copy number, based on phosphorimager scanning of the Northern blots, is approximately 6 $X10^7$ copies of plus-strand/μg of total RNA, and 6 x 10^6 copies of minus strand/ μg of total RNA. The presence of the plus-strand and minus-strand intermediate confirms that the HCV sub-genomic RNA is actively replicating in the S22.3 cell line.

EXAMPLE 3

S22.3 cell line constitutively expresses HCV non-structural proteins.

HCV non-structural protein expression was examined in the S22.3 cell line. Figure 3 displays the result of indirect immunofluorescence that detects the HCV NS4A protein in the S22.3 cell line and not in the replicon negative B1 cell line (a G418 resistant Huh-7 cell line). Indirect immunofluorescence was performed on cells that were cultured and fixed (with 4% paraformaldehyde) onto Lab-tek chamber slides. Cells were permeabilized with 0.2% Triton X-100 for 10 minutes followed by a 1 hour treatment with 5% milk powder dissolved in phosphate-buffered saline (PBS). A rabbit serum containing polyclonal antibody raised against a peptide spanning the HCV NS4A region was the primary antibody used in detection. Following a 2 hour incubation with the primary antibody, cells were washed with PBS and a secondary goat anti-rabbit antibody conjugated with red-fluor Alexa® 594 (Molecular Probes) was added to cells for 3 hours. Unbound secondary antibody was removed with PBS washes and cells were sealed with a cover slip. Figure 3 (top panels) shows the results of immunofluorescence as detected by a microscope with specific fluorescent filtering; the bottom panels represent the identical field of cells viewed by diffractive interference contrast (DIC) microscopy. The majority of S22.3 (Figure 3A) cells within the field stain positively for HCV NS4A protein that localizes in the cytoplasm, whereas the B1 cells (Figure 3B) that fail to express any HCV proteins, only have

background level of staining. A small proportion of S22.3 cells express high levels of intensely stained HCV NS4A.

Expression of the proteins encoded by the bi-cistronic replicon RNA was also examined on Western-blots following SDS-PAGE separation of total proteins extracted from: (i) naïve Huh-7 cell line, (ii) neomycin resistant Huh-7 cell line B1, and (iii) the S22.3 cell line. Figure 4 panels A, B, and C, demonstrate the results of western blots probed with rabbit polyclonal antisera specific for neomycin phosphotransferase (NPT), HCV NS3, and HCV NS5B, respectively. Visualization was achieved through autoradiographic detection of a chemiluminescent reactive secondary HRP-conjugated goat anti-rabbit antibody. Figure 4 panel A shows that the S22.3 RNA replicon cell line, expresses the NPT protein at levels higher than B1 cells (which contain an integrated DNA copy of the *npt* gene) and that the naïve Huh-7 cell line does not produce the NPT protein. Figure 4 panels B and C show that only the S22.3 cell line produces the mature HCV NS3 and NS5B proteins, respectively. The western blots demonstrate that the S22.3 cell line, which harbors actively replicating HCV sub-genomic replicon RNA, maintains replication of the RNA through the high level expression of the HCV non-structural proteins.

EXAMPLE 4

Sequence determination of adapted replicons

Total RNA was extracted from replicon containing Huh7 cells using a RNeasy Kit (Qiagen). Replicon RNA was reverse transcribed and amplified by PCR using a OneStep RT-PCR kit (Qiagen) and HCV specific primers (as selected from the full-length sequence disclosed in WO 00/66623). Ten distinct RT-PCR products, that covered the entire bi-cistronic replicon in a staggered fashion, were amplified using oligonucleotide primers. The PCR fragments were sequenced directly with ABI Prism® BigDye™ Terminator Cycle PCR Sequencing and analyzed on ABI Prism® 377 DNA Sequencer. To analyze the sequence of the HCV replicon 3' and 5' ends a RNA ligation/RT-PCR procedure described in Kolykhalov *et al.* **1996** was followed. The nucleotide sequence of S22.3 is presented as **SEQ ID NO. 2**.

EXAMPLE 5.

Serial Passage of HCV Replicon RNA

The total cellular RNA from the S22.3 cell line was prepared as described above. HCV Replicon RNA copy number was determined by Taqman® RT-PCR analysis and 20 μg of total S22.3 cellular RNA (containing 1 X 10^9 copies of HCV RNA) was transfected by electroporation into 8 X 10^6 naïve Huh-7 cells. Transfected cells were subsequently cultured in 10 cm tissue culture plates containing DMEM supplemented with 10% fetal calf serum (10% FCS). Media was changed to DMEM (10% FCS) supplemented with 1 mg/ml G418 24 hours after transfection and then changed every three days. Twenty-three visible colonies formed three to four weeks post-transfection and G418 selection. G418 resistant colonies were expanded into second generation cell lines that represent the first cell lines harboring serially passaged HCV Replicon RNA. Three of these cell lines: R3, R7, and R16 were the subject of further analyses. First, the efficiency of transduction by each of the adapted replicons was determined by electroporation of the total cellular RNA (extracted from the R3, R7 and R16) into naïve Huh-7 cells; following electroporation, the transduction efficiency was determined as described above, by counting the visible G418 resistant colonies that arose following 3 to 5 weeks of G418 selection (Table 1). Second, the sequence of the serially passed adapted replicons was determined from the total cellular RNA that was extracted from each of the R3, R7 and R16 replicon cell lines as described in example 4 (**SEQ ID NO. 4, 5, 6**). Using the pAPGK12 as a reference sequence (**SEQ ID NO. 1**), the nucleotide changes that were selected in HCV segment of the adapted replicons are presented in Figure 5A. Some of these nucleotide changes are silent and do not change the encoded amino acid whereas others result in an amino acid substitution. Figure 5B summarizes the amino acid changes encoded by the adapted replicons with the amino acid sequence of pAPGK12 as the reference. It is important to note that the reference sequence APGK-12 (SEQ ID NO.1) contains an extra G at the 5'-terminal (5'-GG) that is not maintained in the replicating RNA of the established cell lines. Also noteworthy is that, in addition to G->A at nucleotide 1, there is also an adapted mutation G->C/R at amino acid 2042 (shown as amino acid 1233 in the sequence listing since a.a. 810 of NS2 is numbered as a.a. 1 in SEQ ID) that can be found in all clones analyzed.

TABLE 1

Transfection of Huh-7 cells

RNA	Copies of Replicon	# Colonies	SEQ ID
5 ng APKG12 replicon in 20µg total Huh-7 RNA	1.2×10^9	0	
15 µg APKG12 replicon RNA	3×10^{12}	1 (S22.3)	1
20µg total: S22.3 cellular RNA	3×10^9	**23** (3 clones analyzed)	**2**
R3 cellular RNA	**1×10^9**	**200**	**4**
R7 cellular RNA	1×10^9	20	**5**
R16 cellular RNA	**3×10^8**	**100**	**6**
cloned R3rep RNA	**2.3×10^8**	**2000**	**7**

EXAMPLE 6

Construction of APGK12 with 5' G-> A substitution (APGK12-5'A, SEQ ID NO.24)

The pAPGK12 DNA was modified to change the first nucleotide in the sequence to replace the 5'GG with a 5'A. The change in the pAPGK12 was introduced by replacing an *EcoRI/AgeI* portion of the sequence with a PCR-generated *EcoRI/AgeI* fragment that includes the mutation. The oligonucleotides used for the amplification were (SEQ ID. NO. **20**): 5'-GTG GAC GAA TTC TAA TAC GAC TCA CTA TAA CCA GCC CCC GAT TGG-3' and (SEQ ID. NO. **21**): 5'-GGA ACG CCC GTC GTG GCC AGC CAC GAT-3' and generated a 195 bp DNA fragment that was then digested with *EcoR*I and *Age*I. The resulting 178 bp restriction fragment was used to replace the *EcoR*I / *Age*I fragment in pAPGK12 to generate the pAPGK12-5'A plasmid.

EXAMPLE 7

cDNA CLONING OF THE R3-REPLICON (R3REP).

The cDNA clone of the R3 replicon was produced by RT-PCR of RNA extracted from the R3 cell line. The following two oligonucleotides were used: (**SEQ ID. NO. 22**): 5'-GTC GTC TTC TCT GAC ATG GAG AC-3' and (**SEQ ID. NO. 23**): 5'-GAG TTG

CTC AGT GGA TTG ATG GGC AGC-3'. The ~4400nt PCR fragment, starting within the NS2 coding region and extending to the 5'-end of the NS5B coding region, was cloned into the plasmid pCR3.1 by TA cloning (Invitrogen). The *Sac*II / *Xho*I portion of this R3 sequence was then used to replace the *Sac*II / *Xho*I fragment present in the pAPGK12 and the pAPGK12-5'A described above. Consequently, two R3 cDNA sequences were generated: (I) R3-Rep-5'G with an initiating 5'G **(SEQ ID NO.7)**, and R3-Rep-5'A **(SEQ ID NO.25)** with an initiating 5'A. Sequencing of the R3 rep cDNA identified unique nucleotide changes that differ from the original pAPGK12 sequence (see Figure 5A); some of these changes are silent and do not change the encoded amino acid, whereas others do result in an amino acid change (see Figure 5B). The differences between R3 and the R3-rep reflect the isolation of a unique R3-rep cDNA clone encoding nucleotide changes that were not observed from the sequencing of the total RNA extracted from the R3 cell line.

EXAMPLE 8

Efficiency of colony formation with modified constructs

RNA from pAPGK12, pAPGK12-5'A, pR3-Rep and pR3-Rep-5'A was generated by *in vitro* transcription using the T7 Ribomax® kit (Promega) as described in example 1 above. The reactions containing the pAPGK12-5'A and pR3-Rep-5'A templates were scaled-up 10-fold due to the limitation of commercial RNA polymerase in initiating transcripts with 5'-A. The full length RNAs and control truncated RNA for each clone were introduced into 8 x 10^6 naïve Huh-7 cells by electroporation as described in example 2. Replicon RNA was supplemented with total cellular Huh-7 carrier RNA to achieve a final 15-20µg quantity. The cells were then cultured in DMEM medium supplemented with 10% fetal calf serum and 0.25 mg/ml G418 in two 150 mm plates. The lower concentration of G418 was sufficient to isolate and select replicon containing cell lines as none of the transfectants with the control truncated RNA produced any resistant colonies. In contrast, *in vitro* transcribed APGK-12 RNAs that harbor either a 5'G or 5'A form colonies with the same efficiency (ca. 80 cfu/µg in Figure 6 panels A and B) following selection with G418. Various quantities (ranging from 0.1 ng to 1 µg) of the R3-rep-5'A RNA, were transfected into naïve Huh-7 cells to determine a colony formation efficiency of 1.2 X 10^6 cfu/µg of RNA (Figure 6 panel C depicts transfection with 1 µg of RNA). Various quantities (ranging from 0.1 ng to 1 µg) of R3-rep [5'G] were similarly transfected resulting in a colony formation efficiency of 2 X 10^6 cfu/µg of RNA (Figure 6 panel D

depicts colony formation with 1µg of RNA). Note that, shown for the first time, HCV subgenomic replicons replicate as efficiently with a 5' A nucleotide in place of the 5'G. APGK12 with a 5'A or 5'G RNA have similar transduction efficiencies. Similarly, R3-Rep RNAs with either the 5'A or 5'G both display the markedly increased transduction efficiency. Notably, the adaptive mutants within the HCV non-structural segment encoded by the R3-Rep provides for a substantial increase in transduction efficiency as depicted by the dramatic increase in colony forming units per µg of transfected RNA.

EXAMPLE 9

Quantification of HCV Replicon RNA Levels in Cell lines

S22.3 cells, or cell lines harboring other adapted replicons, were seeded in DMEM supplemented with 10% FBS, PenStrep and 1µg/mL Geneticin. At the end of the incubation period the replicon copy number is evaluated by real-time RT-PCR with the ABI Prism 7700 Sequence Detection System. The TAQMAN® EZ RT-PCR kit provides a system for the detection and analysis of HCV RNA (as first demonstrated by Martell *et al.* **1999** J. Clin. Microbiol. 37: 327-332). Direct detection of the reverse transcription polymerase chain reaction (RT-PCR) product with no downstream processing is accomplished by monitoring the increase in fluorescence of a dye-labeled DNA probe (Figure 6). The nucleotide sequence of both primers (adapted from Ruster, B. Zeuzem, S. and Roth, W.K., **1995**. Analytical Biochemistry 224:597-600) and probe (adapted from Hohne, M., Roeske, H. and Schreier, E. **1998**, Poster Presentation: P297 at the Fifth International Meeting on Hepatitis C Virus and Related Viruses Molecular Virology and Pathogenesis, Venezia-Lido Italy, June 25-28, 1998) located in the 5'-region of the HCV genome are the following:

HCV Forward primer:

5' ACG CAG AAA GCG TCT AGC CAT GGC GTT AGT 3' **(SEQ ID NO.17)**

HCV Reverse primer:

5' TCC CGG GGC ACT CGC AAG CAC CCT ATC AGG 3' **(SEQ ID NO.18)**

HCV Probe:

5' FAM-TGG TCT GCG GAA CGG GTG AGT ACA CC-TAMRA 3' (**SEQ ID NO.19**)

FAM: Fluorescence reporter dye.

TAMRA: Quencher dye.

Using The TAQMAN® EZ RT-PCR kit, the following reaction was set up:

Component	**Volume per sample (µL)**	**Final Concentration**
RNase-Free Water	16	-
5X Taqman EZ Buffer	10	1X
Manganese Acetate 25mM	6	3mM
dATP 10mM	1.5	300µM
dCTP 10mM	1.5	300µM
dGTP 10mM	1.5	300µM
dUTP 20mM	1.5	300µM
HCV Forward Primer 10µM	1	200nM
HCV Reverse Primer 10µM	1	200nM
HCV Probe 5uM	2	200nM
rTth DNA Polymerase 2.5U/µL	2	0.1U/µL
AmpErase UNG 1U/µL	0.5	0.01U/µL
Total Mix	45	-

To this reaction mix, 5µL of total RNA extracted from S22.3 cells diluted at 10ng/µL was added, for a total of 50ng of RNA per reaction. The replicon copy number was evaluated with a standard curve made from known amounts of replicon copies (supplemented with 50ng of wild type Huh-7 RNA) and assayed in an identical reaction mix (Figure 7).

Thermal cycler parameters used for the RT-PCR reaction on the ABI Prism 7700 Sequence Detection System were optimized for HCV detection:

Cycle	Temperature (°C)	Time (Minutes)	Repeat	Reaction
Hold	50	2		Initial Step
Hold	60	30		Reverse Transcription
Hold	95	5		UNG Deactivation
Cycle	95	0:15	2	Melt
	60	1		Anneal/Extend
Cycle	90	0:15	40	Melt
	60	1		Anneal/Extend

Quantification is based on the threshold cycle, where the amplification plot crosses a defined fluorescence threshold. Comparison of the threshold cycles provides a highly sensitive measure of relative template concentration in different samples. Monitoring during early cycles, when PCR fidelity is at its highest, provides precise data for accurate quantification. The relative template concentration can be converted to RNA copy numbers by employing a standard curve of HCV RNA with known copy number (Figure 7).

EXAMPLE 10

A specific HCV NS3 protease anti-viral compound inhibits replication of the HCV replicon in S22.3 cell lines.

In order to determine the effect of a specific HCV NS3 protease anti-viral compound on replicon levels in S22.3 cells, the cells were seeded in 24 Well Cell Culture Cluster at 5 X 10^4 cells per well in 500µL of DMEM complemented with 10% FBS, PenStrep and 1µg/mL Geneticin. Cells were incubated until compound addition in a 5% CO_2 incubator at 37 °C. The dose-response curve of the inhibitor displayed 11 concentrations resulting from serial two-fold dilutions (1:1). The starting concentration of compound A was 100nM. One control well (without any compound) was also included in the course of the experiment. The 24 well plates were incubated for 4 days in a 5% CO_2 incubator at 37 °C. Following a 4 day incubation period, the cells were washed once with PBS and RNA was extracted with the RNeasy® Mini Kit and Qiashredder® from Qiagen. RNA from each well was eluted in 50uL of H_2O. The RNA was quantified by optical density at 260nm on a Cary 1E UV-Visible Spectrophotometer. 50 ng of RNA from each well was used to quantify the HCV replicon RNA copy number as detailed in Example 6. The level of inhibition (% inhibition) of each well containing inhibitor was calculated with the following

equation (CN = HCV Replicon copy number):

$$\%\cdot inhibition = \left(\frac{CN\cdot control - CN\cdot well}{CN\cdot control}\right)*100$$

The calculated % inhibition values were then used to determine IC_{50}, slope factor (n) and maximum inhibition (I_{max}) by the non-linear regression routine NLIN procedure of SAS using the following equation:

$$\%\cdot inhibition = \frac{I_{max}\times[inhibitor]^n}{[inhibitor]^n + IC_{50}{}^n}$$

Compound A was tested in the assay at least 4 times. The IC_{50} curves were analyzed individually by the SAS nonlinear regression analysis. Figure 8 shows a typical curve and Table 2 shows the individual and average IC_{50} values of compound A. The average IC_{50} of compound A in the replication assay was 1.1nM.

TABLE 2

IC_{50} of compound A in the S22.3 Cell line Replicon Assay.

Compound	IC_{50} (nM)	Average IC_{50} (nM)
A	1.2	
	1.2	
	1.0	
	0.9	
		1.1 ± 0.2

DISCUSSION

The reproducible and robust *ex vivo* propagation of hepatitis C virus, to levels required for the accurate testing of potential anti-viral compounds, has not been achieved with any system. As an alternative approach to studying the molecular mechanisms of hepatitis C virus RNA replication, selectable self-replicating bi-cistronic RNAs were developed (Lohman *et al.*, 1999, Science 285:110-113; Bartenschlager CA 2,303,526). Minimally, these replicons encode for some or all of

the non-structural proteins and also carry a selectable marker such as the neomycin phosphotransferase. Though intracellular steady-state levels of these sub-genomic replicon RNAs among the selected clones is moderate to high, the frequency of generating G418-resistant colonies upon transfection of the consensus RNA described by Lohman *et al.* or Bartenschlager is very low. Less than 100 colonies are generated when 8 million cells are transfected with 1 µg of *in vitro* transcribed bi-cistronic replicon RNA. A low efficiency of colony formation was first noted by Lohmann et al (1999 et al, Science 285:110-113). Since then, Lohmann *et al.* (2001), Blight *et al.* (2000), and Guo *et al.* (2001), have isolated sub-genomic RNAs with markedly improved efficiencies in the colony formation assay. Lohmann *et al.*, 1999 originally reported that selection of sub genomic replicons may not involve the selection of adaptive mutants as serially passaged RNA did not demonstrate an improved transfection efficiency. Nevertheless, in an effort to characterize the function and fitness of replicating HCV RNA, we serially passaged the replicon RNA that was isolated from the first selected cell-line. Notably, a significant increase in colony forming efficiency was obtained from this experiment, even though the quantity of replicon RNA was orders of magnitude lower than originally used to transfect the *in vitro* transcribed RNA. Furthermore, a second round serial passage of replicon RNA from this first generation clone into naive Huh-7 cells provided for yet another increase in colony formation efficiency (Table 1).

Our analysis of replicating HCV RNAs identified several adaptive mutations that enhance the efficiency of colony formation by up to 4 orders of magnitude. Adaptive mutations were found in many non-structural proteins, as well as in the 5' non-translated region. The substitution of the 5'-GG doublet for a 5'-A as the inaugurating nucleotide of the HCV 5'-UTR is a variant of the HCV genome that has not been previously described, despite the sequencing of innumerable genotypes and subtypes from across the world. Our original replicon that carried a 5'-GG evolved to variants with either a single 5'-A or 5'-G, both of which showed equal transduction efficiency. We describe here the first report of a HCV genome that can tolerate and stably maintain a 5'A extremity. Moreover, we were successful in re-introducing this defined single nucleotide substitution into our cDNA clone and generate *in vitro* transcribed RNA harboring such an extremity to confirm that a 5'A functions as efficiently as a 5'G.

We have identified adaptive amino acid substitutions in the HCV non-structural proteins NS3, NS4A and NS5A in the R3 replicon, and a substitution in NS5B in the R7 clone (see Figure 5B). These mutations, particularly the combination defined by the R3-rep (**SEQ ID NO. 7**), when reconstituted into a cDNA clone and transcribed onto a RNA replicon, result in a significantly enhanced transduction efficiency of up to 20,000 fold from the original wild type APGK12 replicon RNA. However, the steady state levels of intracellular replicon RNA were comparable from each of the different isolated clones. This result suggests that the increase in replication efficiency by the adaptive mutations does not result in higher stable intracellular RNA levels due to higher RNA replication, but rather confers increased permissivity for establishing the replicon in a greater number of Huh7 cells. Such a phenotype may be manifested transiently, through an initial increase of the amount of *de novo* replication, that is required to surpass a defined threshold to establish persistently replicating RNAs within a population of dividing cells.

Recently three other groups also identified other distinct adaptive mutants. Lohmann *et al.* (2000) reported enhanced transduction efficiencies of up to 10,000 fold with mutations in NS3, NS4B, NS5A and NS5B. Blight *et al.* (2000) reported an augmentation of transduction efficiencies up to 20,000 fold with a single mutation in NS5A whereas Guo *et al.* (2001) reported increases in transduction efficiencies of 5,000-10,000 fold with a deletion of a single amino acid in NS5A. The amino acid substitutions that we describe here have not previously been identified as adaptive mutants that enhance the efficiency of RNA transfection and/or replication. One exception is the mutation of E1202G in NS3 that we found in both the R7 and R16 replicons. This adaptation was previously described by Guo et al (2001) and Krieger et al (2001). All other adaptive mutations, without exception, described herein are unpublished.

The development of selectable subgenomic HCV replicons has provided for potential avenues of exploration on HCV RNA replication, persistence, and pathogenesis in cultured cells. However, the low transduction efficiency with the HCV RNA-containing replicons as originally described (Lohmann *et al.*, 1999) showed that it was not a practical system for reverse genetics studies. The adaptive mutants described herein overcome the low transduction efficiency. In light of the recent descriptions of adaptive mutants by other groups, we note that adaptation can be

achieved by distinct mutations in different HCV NS proteins, although the level of adaptation can vary drastically. The replicons encoding adaptive mutants that are described herein are ideally suited for reverse genetic studies to identify novel HCV targets or host cell targets that may modulate HCV RNA replication or HCV replicon RNA colony formation. The adapted and highly efficient replicons are suitable tools for characterizing subtle genotypic or phenotypic changes that affect an easily quantifiable transduction efficiency.

Lastly, we have used our adapted HCV sub genomic replicon cell-line to demonstrate the proficient inhibition of HCV RNA replication by a specific small molecule inhibitor of the HCV NS3 protease. This is the first demonstration that an antiviral, designed to specifically inhibit one of the HCV non-structural proteins, inhibits HCV RNA replication in cell culture. Moreover, this compound and our S22.3 cell line validate the proposal that RNA replication is directed by the HCV non-structural proteins NS3 to NS5B. The assay that we have described and validated will be extremely useful in characterizing other inhibitors of HCV non-structural protein function in cell culture in a high throughput fashion.

All references found throughout the present disclosure are herein incorporated by reference whether they be found in the following list or not.

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CLAIMS

1. A HCV polynucleotide molecule comprising a 5'-non translated region (NTR) wherein guanine at position 1 is substituted for adenine.

2. A HCV self-replicating polynucleotide comprising:
   - a 5'-NTR consisting of ACCAGC (SEQ ID NO. 8);
   - a HCV polyprotein region coding for a HCV polyprotein; and
   - a 3'-NTR region.

3. The HCV polynucleotide according to claim 2, wherein said polyprotein comprises one or more amino acid substitution selected from the group consisting of: R(1135)K; S(1148)G; S(1560)G; K(1691)R; L(1701)F; I(1984)V; T(1993)A; G(2042)C; G(2042)R; S(2404)P; L(2155)P; P(2166)L and M(2992)T.

4. The HCV polynucleotide encoding a polyprotein comprising one or more of the amino acid substitution as defined in claim 3, and further comprising the amino acid substitution E(1202)G.

5. The HCV polynucleotide according to claim 3, wherein said substitution is a G2042C or a G2042R mutation.

6. The HCV polynucleotide according to claim 3, wherein said substitution is selected from the group consisting of: K(1691)R; and G(2042)C.

7. The HCV polynucleotide according to claim 3, wherein said substitution is selected from the group consisting of: R(1135)K; S(1560)G; K(1691)R; T(1993)A; G(2042)C; and P(2166)L.

8. The HCV polynucleotide according to claim 3, wherein said substitution is selected from the group consisting of: R(1135)K; S(1560)G; K(1691)R; T(1993)A; G(2042)C; L(2155)P; and P(2166)L.

9. The HCV polynucleotide according to claim 3, wherein said substitution is selected

from the group consisting of: E(1202)G; I(1984)V; G(2042)C; and M(2992)T.

10. The HCV polynucleotide according to claim 3, wherein said substitution is selected from the group consisting of: S(1148)G; E(1202)G; L(1701)F; G(2042)R; and S(2404)P.

11. The HCV polynucleotide according to claim 2, wherein said polynucleotide is a RNA molecule encoded by the DNA molecule selected from the group consisting of: SEQ ID NO. 2, 4, 5, 6, 7, 24 and 25.

12. The HCV polynucleotide according to claim 2, wherein said polynucleotide is a DNA molecule selected from the group consisting of: SEQ ID NO. 2, 4, 5, 6, 7, 24 and 25.

13. An expression vector comprising a DNA form of the polynucleotide according to claim 2, operably linked to a promoter.

14. A host cell transfected with the self-replicating polynucleotide molecule according to claim 2.

15. A host cell according to claim 14, wherein the host cell is a eukaryotic cell line.

16. A host cell according to claim 15, wherein said eukaryotic cell line is a hepatic cell line.

17. A host cell according to claim 16, wherein said hepatic cell line is Huh-7.

18. A RNA replication assay comprising the steps of:

a) incubating the host cell according to claim 14 under conditions suitable for RNA replication;

b) isolating the total cellular RNA from the cells; and

c) analyzing the RNA so as to measure the amount of HCV RNA replicated.

19. The assay according to claim 18, wherein the analysis of RNA levels in step c) is carried out by amplifying the RNA by real-time RT-PCR analysis using HCV specific primers so as to measure the amount of HCV RNA replicated.

20. The assay according to claim 18, wherein said polynucleotide encodes for a reporter gene, and the analysis of RNA levels in step c) is carried out by assessing the level of reporter expressed.

21. A method for testing a compound for inhibiting HCV replication, including the steps of:

a) carrying step a) according to claim 18, in the presence or absence of the compound;

b) isolating the total cellular RNA from the cells; and

c) analyzing the RNA so as to measure the amount of HCV RNA replicated.

d) comparing the levels of HCV RNA in cells in the absence and presence of the inhibitor,

wherein reduced RNA levels is indicative of the ability of the compound to inhibit replication.

22. The method according to claim 21, wherein said cell line is incubated with the test compound for about 3-4 days at a temperature of about 37°C.

23. A HCV polynucleotide molecule comprising:

- a 5'-NTR region;
- a HCV polyprotein region coding for a HCV polyprotein comprising one or more amino acid substitution selected from the group consisting of: R(1135)K; S(1148)G; S(1560)G; K(1691)R; L(1701)F; I(1984)V; T(1993)A; G(2042)C; G(2042)R; S(2404)P; L(2155)P; P(2166)L and M(2992)T; and
- a 3'-NTR region.

24. The HCV self-replicating polynucleotide encoding a polyprotein comprising the any one of the amino acid substitutions as defined in claim 24, further comprising the amino acid substitution E(1202)G.

25. The polynucleotide according to claim 24, wherein said substitution is a G2042C or a G2042R mutation.

26. The HCV polynucleotide according to claim 24, wherein said substitution is selected

from the group consisting of: K(1691)R; and G(2042)C.

27. The HCV polynucleotide according to claim 24, wherein said substitution is selected from the group consisting of: R(1135)K; S(1560)G; K(1691)R; T(1993)A; G(2042)C; and P(2166)L.

28. The HCV polynucleotide according to claim 24, wherein said substitution is selected from the group consisting of: R(1135)K; S(1560)G; K(1691)R; T(1993)A; G(2042)C; L(2155)P; and P(2166)L.

29. The HCV polynucleotide according to claim 24, wherein said substitution is selected from the group consisting of: E(1202)G; I(1984)V; G(2042)C; and M(2992)T.

30. The HCV polynucleotide according to claim 24, wherein said substitution is selected from the group consisting of: S(1148)G; E(1202)G; L(1701)F; G(2042)R; and S(2404)P.

31. The HCV polynucleotide according to claim 24, wherein said molecule is a RNA molecule encoded by the DNA molecule selected from the group consisting of: SEQ ID NO. 2, 4, 5, 6, 7, 24 and 25.

32. The HCV polynucleotide according to claim 24, wherein said molecule is a DNA molecule selected from the group consisting of: SEQ ID NO. 2, 4, 5, 6, 7, 24 and 25.

33. An expression vector comprising a DNA form of the polynucleotide according to claim 24, operably linked to a promoter.

34. A host cell transfected with the self-replicating polynucleotide according to claim 24.

35. A host cell according to claim 34, wherein the host cell is a eukaryotic cell line.

36. A host cell according to claim 35, wherein said eukaryotic cell line is a hepatic cell line.

37. A host cell according to claim 36, wherein said hepatic cell line is Huh-7.

38. A RNA replication assay comprising the steps of:

incubating the host cell according to claim 34 under conditions suitable for RNA replication;

isolating the total cellular RNA from the cells; and

analyzing the RNA so as to measure the amount of HCV RNA replicated.

39. The assay according to claim 38, wherein the analysis of RNA levels in step c) is carried out by amplifying the RNA by real-time RT-PCR analysis using HCV specific primers so as to measure the amount of HCV RNA replicated.

40. The assay according to claim 38, wherein said polynucleotide encodes for a reporter gene, and the analysis of RNA levels in step c) is carried out by assessing the level of reporter expressed.

41. A method for testing a compound for inhibiting HCV replication, including the steps of:

a) carrying step a) according to claim 38, in the presence or absence of the compound;

b) isolating the total cellular RNA from the cells; and

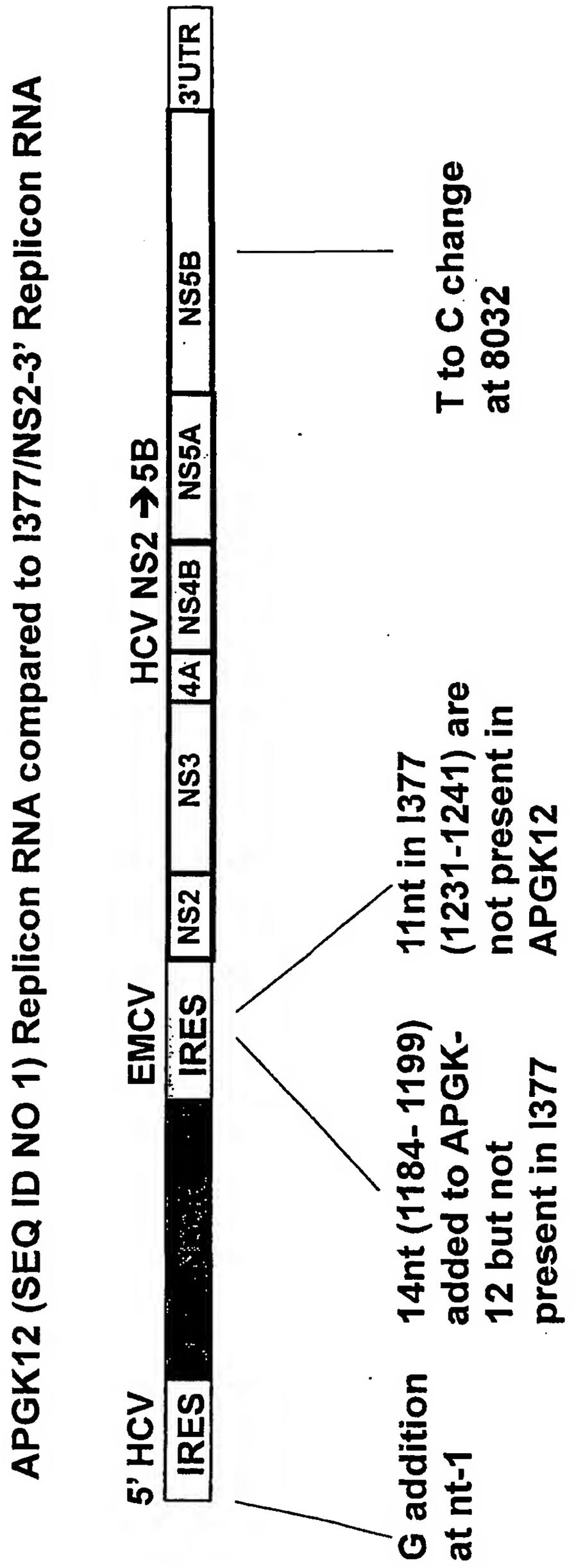
c) analyzing the RNA so as to measure the amount of HCV RNA replicated.

d) comparing the levels of HCV RNA in cells in the absence and presence of the inhibitor,

wherein reduced RNA levels is indicative of the ability of the compound to inhibit replication.

42. The method according to claim 41, wherein said cell line is incubated with the test compound for about 3-4 days at a temperature of about 37°C.

FIGURE 1


APGK12 (SEQ ID NO 1) Replicon RNA compared to I377/NS2-3' Replicon RNA
5' HCV
IRES
EMCV
IRES
NS2
NS3
4A
HCV NS2 → 5B
NS4B
NS5A
NS5B
3'UTR
G addition at nt-1
14nt (1184- 1199) added to APGK-12 but not present in I377
11nt in I377 (1231-1241) are not present in APGK12
T to C change at 8032

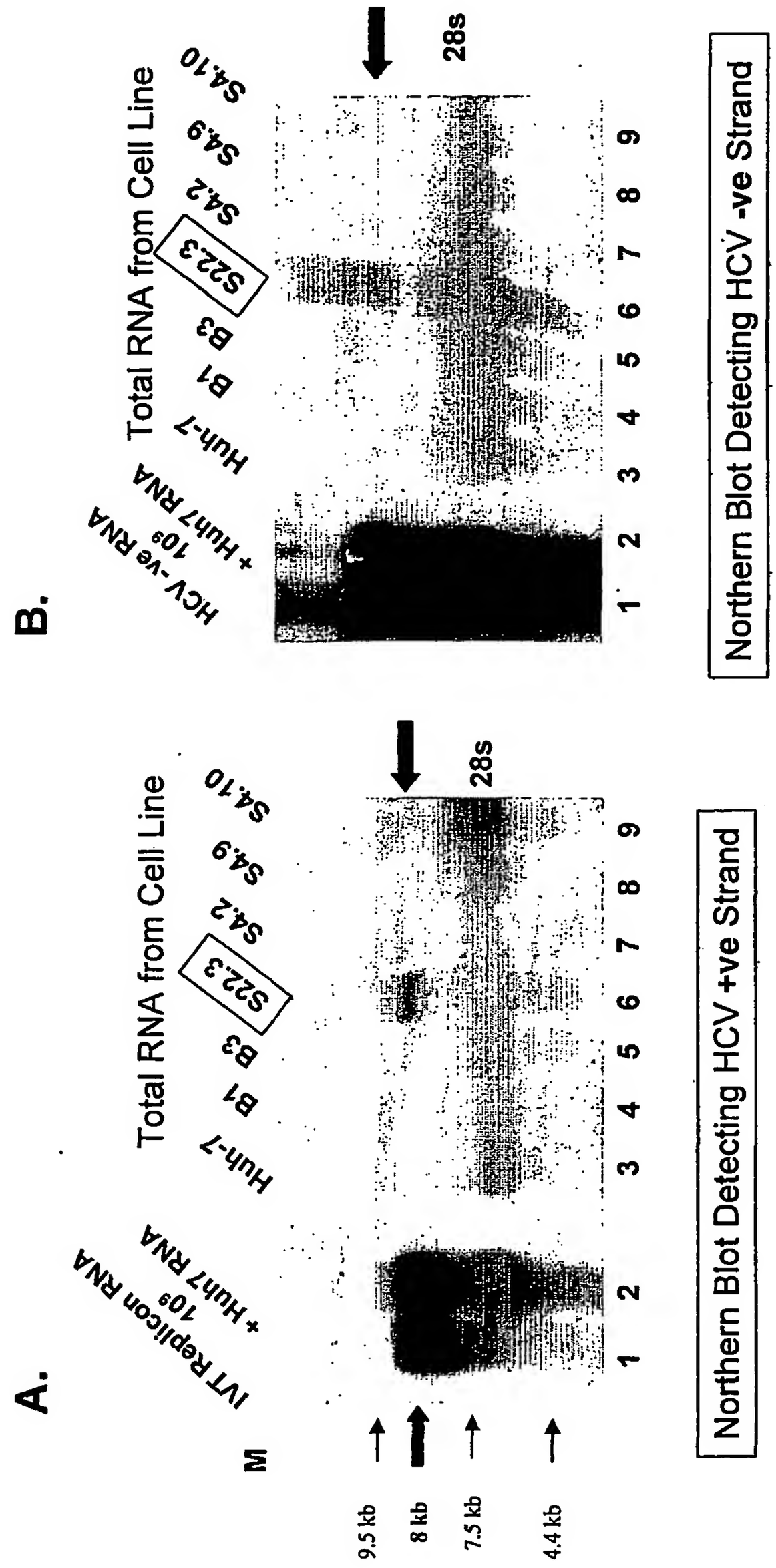

A.
IVT Replicon RNA
10⁹
+ Huh7 RNA
Total RNA from Cell Line
Huh-7
B1
B3
S22.3
S4.2
S4.9
S4.10
M
1
2
3
4
5
6
7
8
9
28s
9.5 kb
8 kb
7.5 kb
4.4 kb
Northern Blot Detecting HCV +ve Strand
B.
HCV -ve RNA
10⁹
+ Huh7 RNA
Total RNA from Cell Line
Huh-7
B1
B3
S22.3
S4.2
S4.9
S4.10
1
2
3
4
5
6
7
8
9
28s
Northern Blot Detecting HCV -ve Strand

FIGURE 2

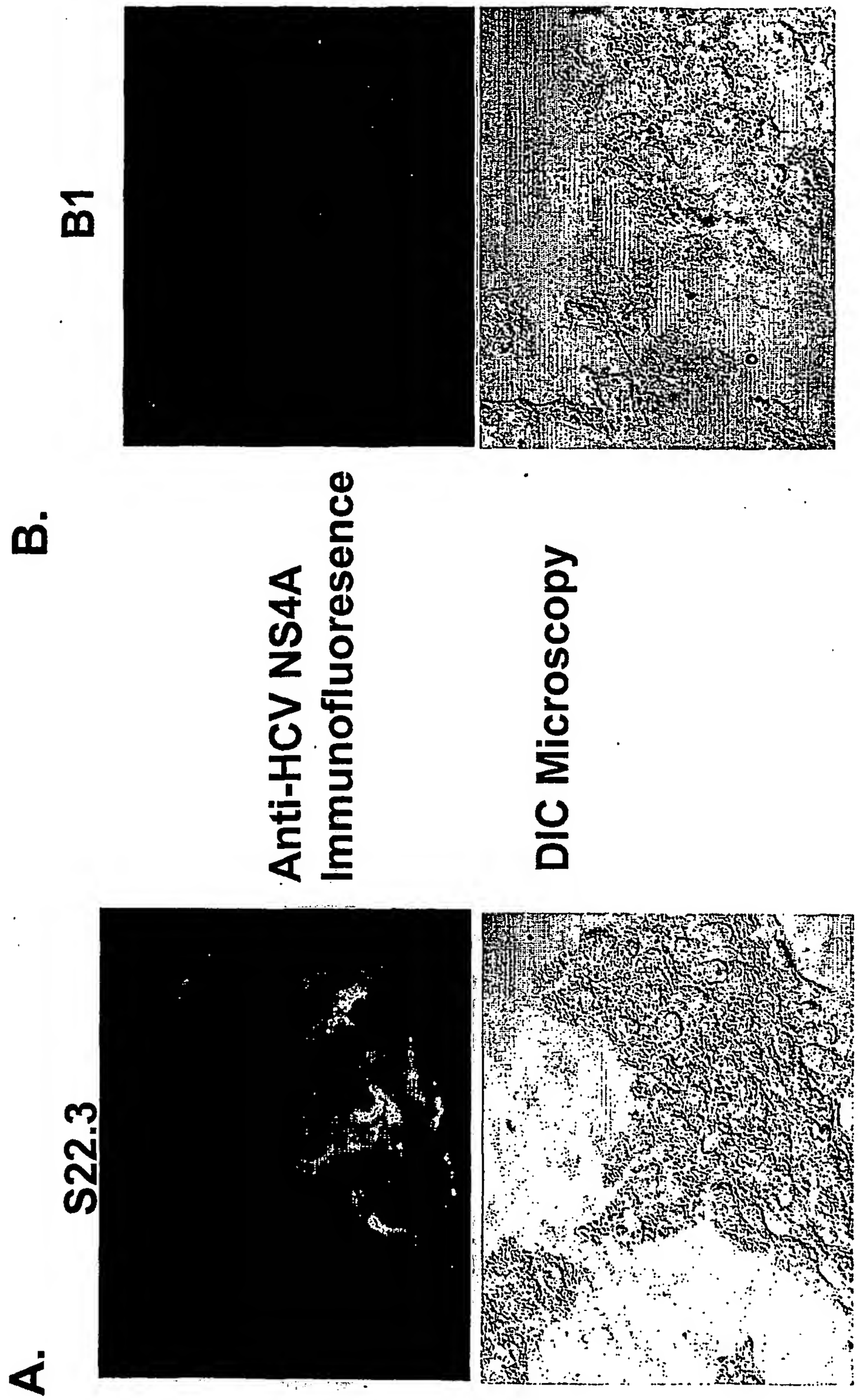


FIGURE 3

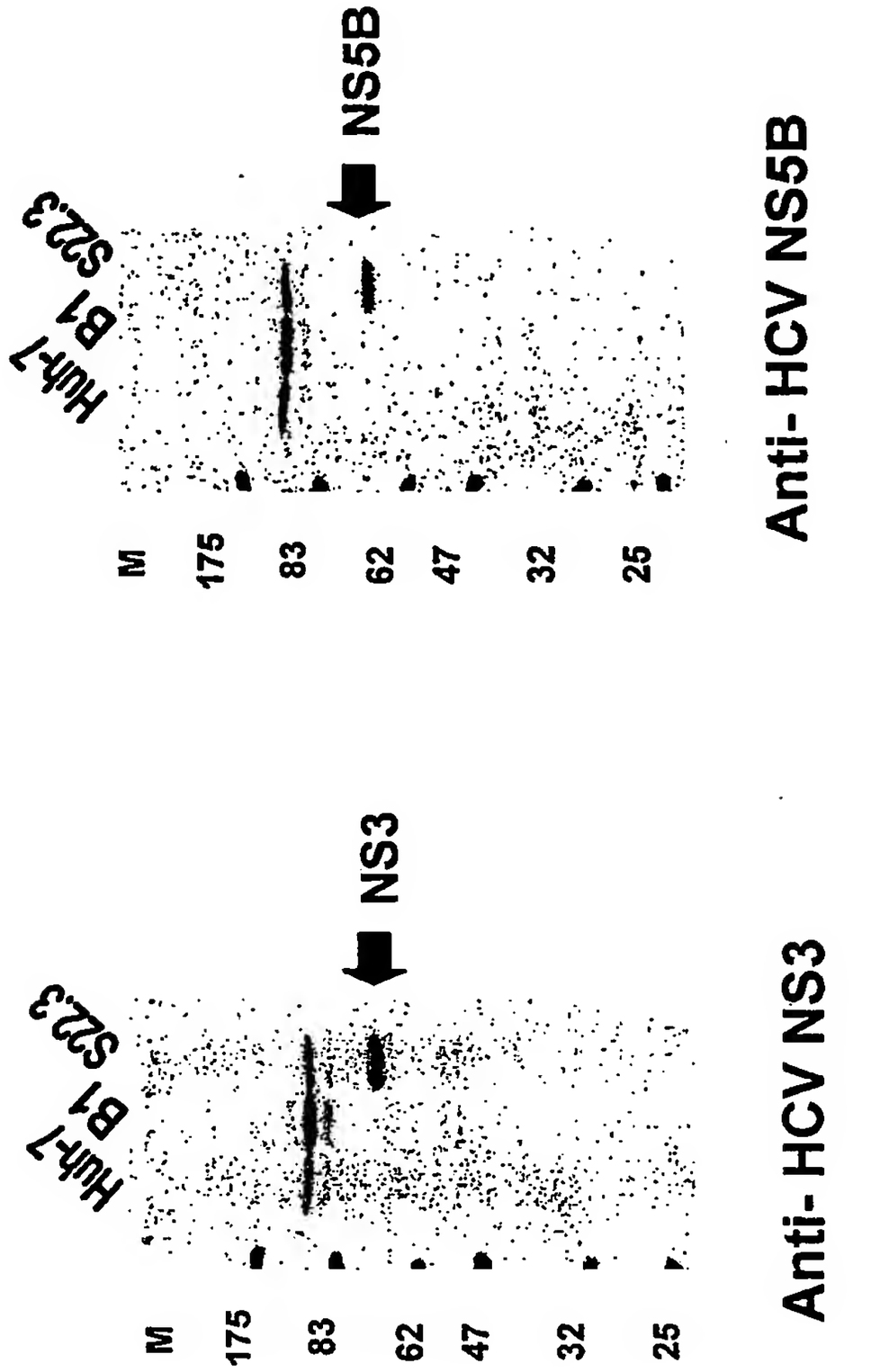

C.
NS5B
Huh7 B1 S22.3
M
175
83
62
47
32
25
Anti- HCV NS5B
B.
NS3
Huh7 B1 S22.3
M
175
83
62
47
32
25
Anti- HCV NS3
A.
NPT
Huh7 B1 S22.3
M
175
83
62
47
32
25
Anti- Neomycin Phosphotransferase

FIGURE 4

FIGURE 5A

	S 22-3 SEQ ID NO 2	R3 SEQ ID NO. 4	R3-rep SEQ ID NO. 7	R7 SEQ ID NO. 5	R16 SEQ ID NO 6
5'end - FIRST nt (HCV IRES)	*G (nt 1) A	G (nt 1) A	-	-	G (nt 1) A
Neo	-	A (nt 461) G	-	-	-
EMCV IRES	-	A (nt 1739) G	-	-	-
NS 2	-	-	-	-	-
NS 3	-	G (nt 2778) A A (nt 2840) C A (nt 4052) G	T (nt 2509) C G (nt 2778) A A (nt 2840) C T (nt 3574) C A (nt 4052) G	A (nt 2935) G A (nt 2979) G	A (nt 2816) G A (nt 2979) G
NS 4A	A (nt 4446) R	A (nt 4446) G	C (nt 4387) T A (nt 4446) G C (nt 4507) T	-	C (nt 4475) T
NS 4B	-	T (nt 4855) C	T (nt 4855) C	-	-
NS 5A	G (nt 5498) T A (nt 6268) R	A (nt 5351) G G (nt 5498) T G (nt 5659) A C (nt 5871) T A (nt 6268) G	A (nt 5351) G G (nt 5498) T G (nt 5659) A T (nt 5838) C C (nt 5871) T A (nt 6115) G	A (nt 5324) G G (nt 5498) T T (nt 6001) C	G (nt 5498) C T (nt 6320) C T (nt 6584) C
NS 5B	-	A (nt 6662) G	-	C (nt 7252) T T (nt 8349) C	-
3'end - last 98 nt	-	-	-	-	-

*first nt = G from HCV ires

FIGURE 5B

	S 22-3 SEQ ID NO. 2	R3 SEQ ID NO. 4	R3 Rep SEQ ID NO. 7	R7 SEQ ID NO. 5	R16 SEQ ID NO. 6
5'end - FIRST nt (HCV IRES)	G (nt 1) A	G (nt 1) A	-	-	G (nt 1) A
NS 2	-	-	-	-	-
NS 3	-	R (1135) K S (1560) G	R (1135) K S (1560) G	E (1202) G	S (1148) G E (1202) G
NS 4A	K (1691) mix K/R	K (1691) R	K (1691) R	-	L (1701) F
NS 4B	-	-	-	-	-
NS 5A	G (2042) C	T (1993) A G (2042) C P (2166) L	T (1993) A G (2042) C L (2155) P P (2166) L	I (1984) V G (2042) C	G (2042) R S (2404) P
NS 5B	-	-	-	M (2992) T	-
3'end - last 98 nt	-	-	-	-	-

first a.a. of NS2 = 810

FIGURE 6

AMINO ACID SUBSTITUTIONS

CLONE APGK-12												
5' HCV		EMCV	HCV NS2→5B						3'HCV			
IRES	NeoR	IRES	NS2	NS3	4A	NS4B	NS5A	NS5B	UTR			
G (nt1) SEQ ID NO 1												
A (nt1) SEQ ID NO 24												
R3 rep A(nt1) SEQ ID NO 25				R(1135)K S(1560)G	K(1691)R	-	T(1993)A G(2042)C L(2155)P P(2166)L					
G(nt1) SEQ ID NO 7				R(1135)K S(1560)G	K(1691)R	-	T(1993)A G(2042)C L(2155)P P(2166)L					

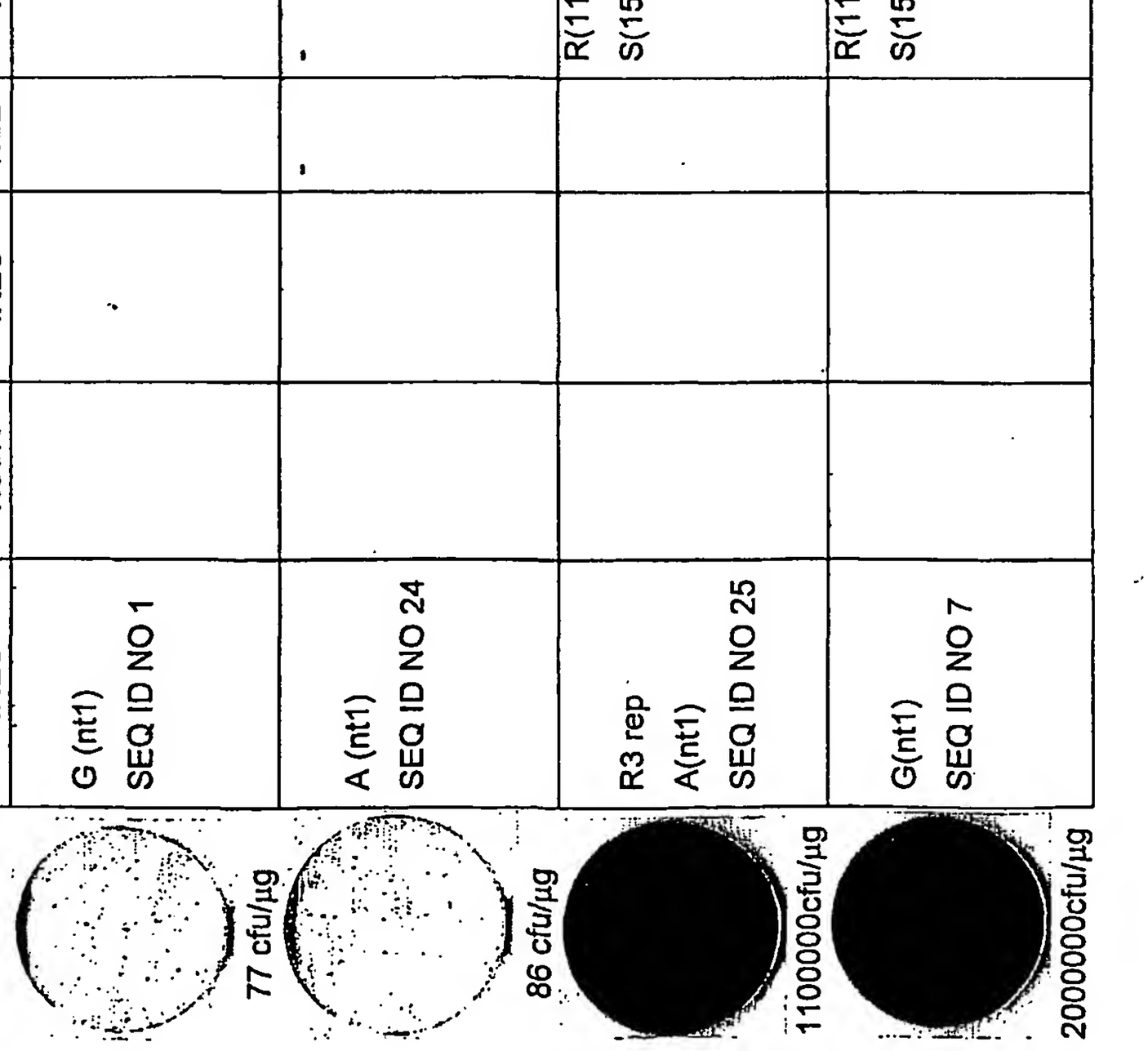
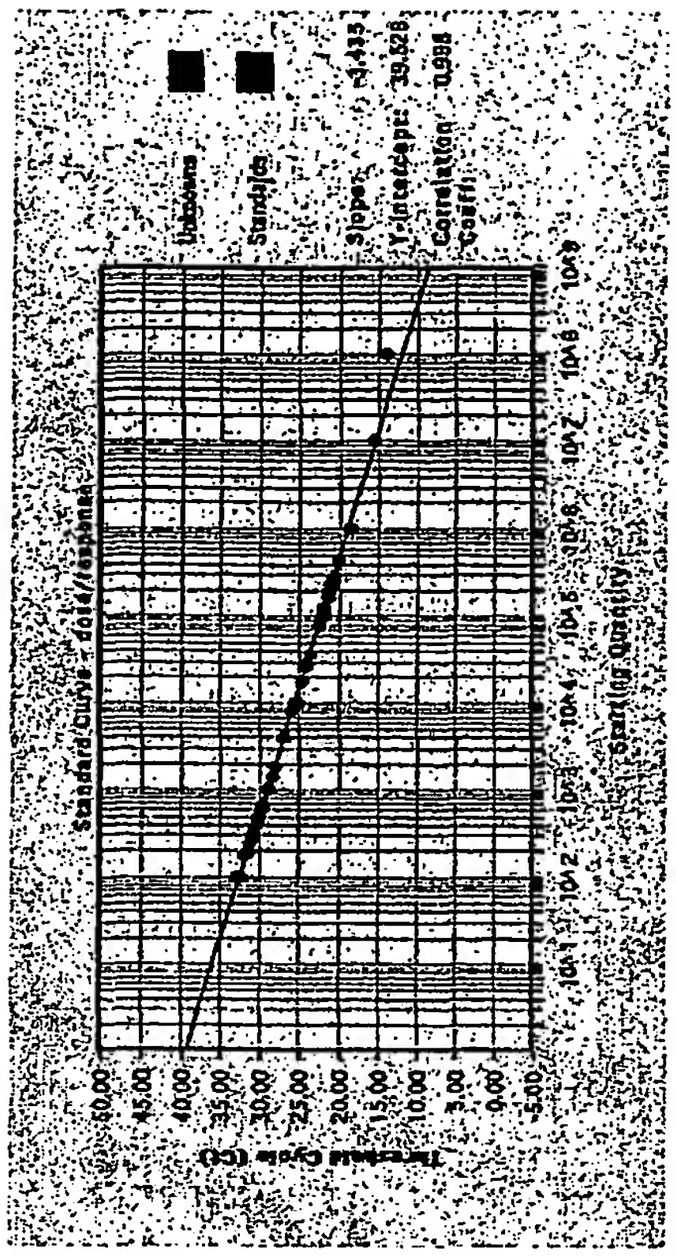
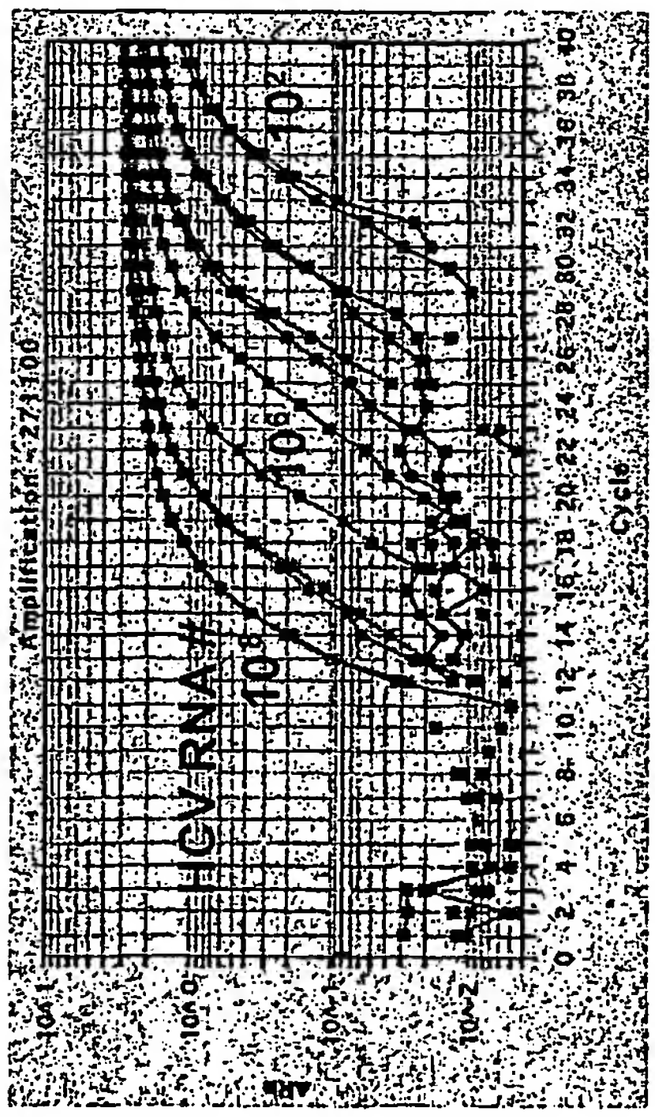


FIGURE 7

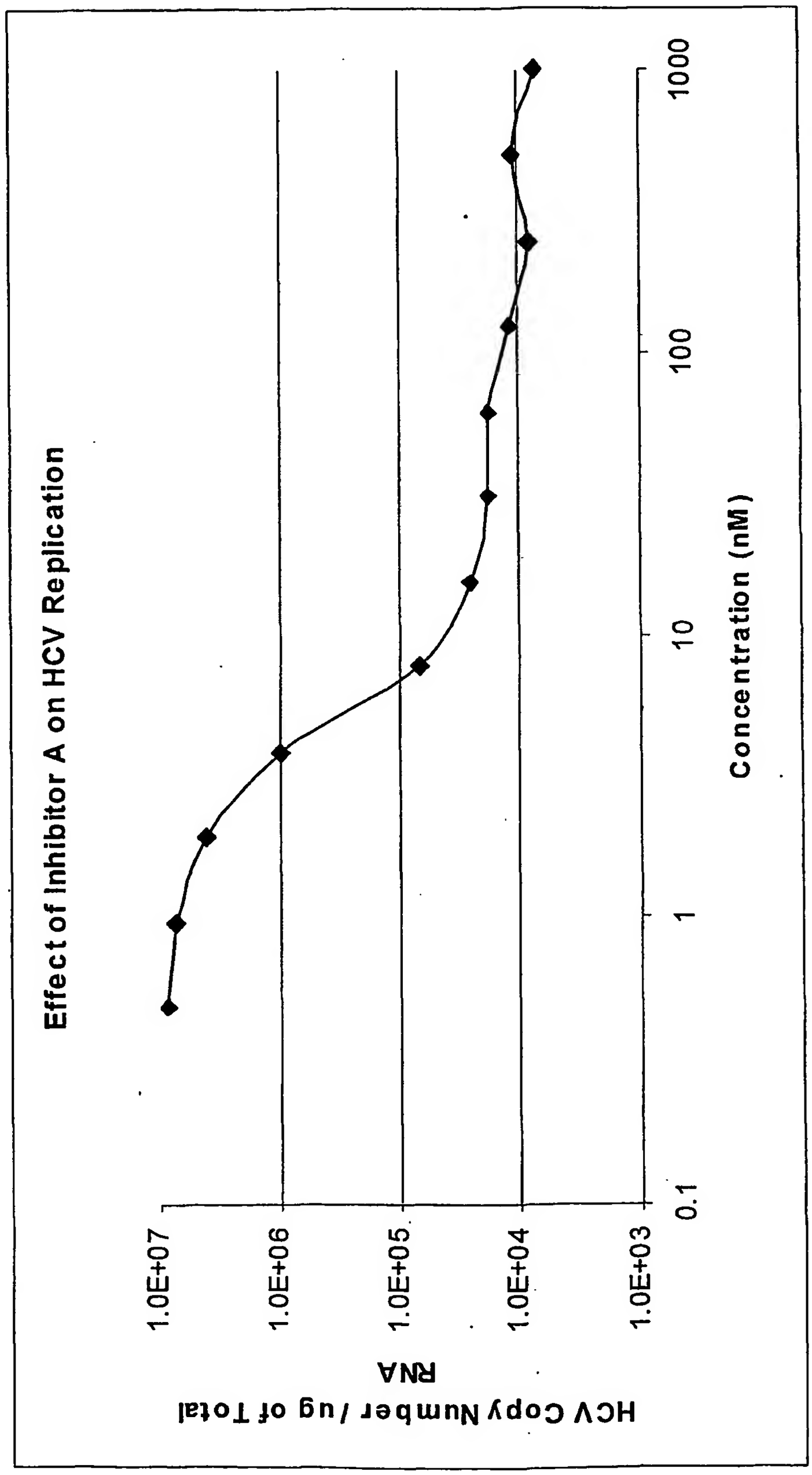
HCV-Replicon: RNA Quantification





Ct = Threshold cycle α Starting RNA Quantity

FIGURE 8


Effect of Inhibitor A on HCV Replication
HCV Copy Number / ug of Total RNA
1.0E+07
1.0E+06
1.0E+05
1.0E+04
1.0E+03
0.1
1
10
100
1000
Concentration (nM)

SEQUENCE LISTING

<110> BOEHRINGER INGELHEIM (CANADA) LTD.

<120> SELF REPLICATING RNA MOLECULE FROM HEPATITIS C VIRUS

<130> 13/083

<150> 60/257,857
<151> 2000-12-22

<160> 25

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 8639
<212> DNA
<213> HCV

<220>
<221> CDS
<222> (1803)...(8408)

<400> 1
ggccagcccc cgattggggg cgacactcca ccatagatca ctcccctgtg aggaactact 60
gtcttcacgc agaaagcgtc tagccatggc gttagtatga gtgtcgtgca gcctccagga 120
ccccccctcc cgggagagcc atagtggtct gcggaaccgg tgagtacacc ggaattgcca 180
ggacgaccgg gtcctttctt ggatcaaccc gctcaatgcc tggagatttg ggcgtgcccc 240
cgcgagactg ctagccgagt agtgttgggt cgcgaaaggc cttgtggtac tgcctgatag 300
ggtgcttgcg agtgccccgg gaggtctcgt agaccgtgca ccatgagcac gaatcctaaa 360
cctcaaagaa aaaccaaagg gcgcgccatg attgaacaag atggattgca cgcaggttct 420
ccggccgctt gggtggagag gctattcggc tatgactggg cacaacagac aatcggctgc 480
tctgatgccg ccgtgttccg gctgtcagcg caggggcgcc cggttctttt tgtcaagacc 540
gacctgtccg gtgccctgaa tgaactgcag gacgaggcag cgcggctatc gtggctggcc 600
acgacgggcg ttccttgcgc agctgtgctc gacgttgtca ctgaagcggg aagggactgg 660
ctgctattgg gcgaagtgcc ggggcaggat ctcctgtcat ctcaccttgc tcctgccgag 720
aaagtatcca tcatggctga tgcaatgcgg cggctgcata cgcttgatcc ggctacctgc 780
ccattcgacc accaagcgaa acatcgcatc gagcgagcac gtactcggat ggaagccggt 840
cttgtcgatc aggatgatct ggacgaagag catcaggggc tcgcgccagc cgaactgttc 900
gccaggctca aggcgcgcat gcccgacggc gaggatctcg tcgtgaccca tggcgatgcc 960
tgcttgccga atatcatggt ggaaaatggc cgcttttctg gattcatcga ctgtggccgg 1020
ctgggtgtgg cggaccgcta tcaggacata gcgttggcta cccgtgatat tgctgaagag 1080
cttggcggcg aatgggctga ccgcttcctc gtgctttacg gtatcgccgc tcccgattcg 1140
cagcgcatcg ccttctatcg ccttcttgac gagttcttct gagttcgcgc ccagatgtta 1200
acagaccaca acggtttccc tctagcggga tcaattccgc ccccccccct aacgttactg 1260
gccgaagccg cttggaataa ggccggtgtg cgtttgtcta tatgttattt tccaccatat 1320
tgccgtcttt tggcaatgtg agggcccgga aacctggccc tgtcttcttg acgagcattc 1380
ctaggggtct ttcccctctc gccaaaggaa tgcaaggtct gttgaatgtc gtgaaggaag 1440
cagttcctct ggaagcttct tgaagacaaa caacgtctgt agcgaccctt tgcaggcagc 1500
ggaacccccc acctggcgac aggtgcctct gcggccaaaa gccacgtgta taagatacac 1560
ctgcaaaggc ggcacaaccc cagtgccacg ttgtgagttg gatagttgtg gaaagagtca 1620
aatggctctc ctcaagcgta ttcaacaagg ggctgaagga tgcccagaag gtaccccatt 1680
gtatgggatc tgatctgggg cctcggtgca catgctttac atgtgtttag tcgaggttaa 1740
aaaacgtcta ggccccccga accacgggga cgtggttttc ctttgaaaaa cacgataata 1800

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cc atg gac cgg gag atg gca gca tcg tgc gga ggc gcg gtt ttc gta    1847
   Met Asp Arg Glu Met Ala Ala Ser Cys Gly Gly Ala Val Phe Val
    1               5                  10                  15

ggt ctg ata ctc ttg acc ttg tca ccg cac tat aag ctg ttc ctc gct  1895
Gly Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala
                20                  25                  30

agg ctc ata tgg tgg tta caa tat ttt atc acc agg gcc gag gca cac  1943
Arg Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His
            35                  40                  45

ttg caa gtg tgg atc ccc ccc ctc aac gtt cgg ggg ggc cgc gat gcc  1991
Leu Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala
        50                  55                  60

gtc atc ctc ctc acg tgc gcg atc cac cca gag cta atc ttt acc atc  2039
Val Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile
    65                  70                  75

acc aaa atc ttg ctc gcc ata ctc ggt cca ctc atg gtg ctc cag gct  2087
Thr Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala
80                  85                  90                  95

ggt ata acc aaa gtg ccg tac ttc gtg cgc gca cac ggg ctc att cgt  2135
Gly Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg
                100                 105                 110

gca tgc atg ctg gtg cgg aag gtt gct ggg ggt cat tat gtc caa atg  2183
Ala Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met
            115                 120                 125

gct ctc atg aag ttg gcc gca ctg aca ggt acg tac gtt tat gac cat  2231
Ala Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His
        130                 135                 140

ctc acc cca ctg cgg gac tgg gcc cac gcg ggc cta cga gac ctt gcg  2279
Leu Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala
    145                 150                 155

gtg gca gtt gag ccc gtc gtc ttc tct gat atg gag acc aag gtt atc  2327
Val Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile
160                 165                 170                 175

acc tgg ggg gca gac acc gcg gcg tgt ggg gac atc atc ttg ggc ctg  2375
Thr Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu
                180                 185                 190

ccc gtc tcc gcc cgc agg ggg agg gag ata cat ctg gga ccg gca gac  2423
Pro Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp
            195                 200                 205

agc ctt gaa ggg cag ggg tgg cga ctc ctc gcg cct att acg gcc tac  2471
Ser Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr
        210                 215                 220
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tcc caa cag acg cga ggc cta ctt ggc tgc atc atc act agc ctc aca   2519
Ser Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr
    225                 230                 235

ggc cgg gac agg aac cag gtc gag ggg gag gtc caa gtg gtc tcc acc   2567
Gly Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr
240                 245                 250                 255

gca aca caa tct ttc ctg gcg acc tgc gtc aat ggc gtg tgt tgg act   2615
Ala Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr
                260                 265                 270

gtc tat cat ggt gcc ggc tca aag acc ctt gcc ggc cca aag ggc cca   2663
Val Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro
            275                 280                 285

atc acc caa atg tac acc aat gtg gac cag gac ctc gtc ggc tgg caa   2711
Ile Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln
        290                 295                 300

gcg ccc ccc ggg gcg cgt tcc ttg aca cca tgc acc tgc ggc agc tcg   2759
Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser
    305                 310                 315

gac ctt tac ttg gtc acg agg cat gcc gat gtc att ccg gtg cgc cgg   2807
Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg
320                 325                 330                 335

cgg ggc gac agc agg ggg agc cta ctc tcc ccc agg ccc gtc tcc tac   2855
Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr
                340                 345                 350

ttg aag ggc tct tcg ggc ggt cca ctg ctc tgc ccc tcg ggg cac gct   2903
Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala
            355                 360                 365

gtg ggc atc ttt cgg gct gcc gtg tgc acc cga ggg gtt gcg aag gcg   2951
Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala
        370                 375                 380

gtg gac ttt gta ccc gtc gag tct atg gaa acc act atg cgg tcc ccg   2999
Val Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro
    385                 390                 395

gtc ttc acg gac aac tcg tcc cct ccg gcc gta ccg cag aca ttc cag   3047
Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln
400                 405                 410                 415

gtg gcc cat cta cac gcc cct act ggt agc ggc aag agc act aag gtg   3095
Val Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val
                420                 425                 430

ccg gct gcg tat gca gcc caa ggg tat aag gtg ctt gtc ctg aac ccg   3143
Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro
            435                 440                 445
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tcc gtc gcc gcc acc cta ggt ttc ggg gcg tat atg tct aag gca cat   3191
Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His
        450                 455                 460

ggt atc gac cct aac atc aga acc ggg gta agg acc atc acc acg ggt   3239
Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly
    465                 470                 475

gcc ccc atc acg tac tcc acc tat ggc aag ttt ctt gcc gac ggt ggt   3287
Ala Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly
480                 485                 490                 495

tgc tct ggg ggc gcc tat gac atc ata ata tgt gat gag tgc cac tca   3335
Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser
                500                 505                 510

act gac tcg acc act atc ctg ggc atc ggc aca gtc ctg gac caa gcg   3383
Thr Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala
            515                 520                 525

gag acg gct gga gcg cga ctc gtc gtg ctc gcc acc gct acg cct ccg   3431
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro
        530                 535                 540

gga tcg gtc acc gtg cca cat cca aac atc gag gag gtg gct ctg tcc   3479
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser
    545                 550                 555

agc act gga gaa atc ccc ttt tat ggc aaa gcc atc ccc atc gag acc   3527
Ser Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Thr
560                 565                 570                 575

atc aag ggg ggg agg cac ctc att ttc tgc cat tcc aag aag aaa tgt   3575
Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys
                580                 585                 590

gat gag ctc gcc gcg aag ctg tcc ggc ctc gga ctc aat gct gta gca   3623
Asp Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Leu Asn Ala Val Ala
            595                 600                 605

tat tac cgg ggc ctt gat gta tcc gtc ata cca act agc gga gac gtc   3671
Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val
        610                 615                 620

att gtc gta gca acg gac gct cta atg acg ggc ttt acc ggc gat ttc   3719
Ile Val Val Ala Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe
    625                 630                 635

gac tca gtg atc gac tgc aat aca tgt gtc acc cag aca gtc gac ttc   3767
Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe
640                 645                 650                 655

agc ctg gac ccg acc ttc acc att gag acg acg acc gtg cca caa gac   3815
Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp
                660                 665                 670
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gcg gtg tca cgc tcg cag cgg cga ggc agg act ggt agg ggc agg atg   3863
Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met
            675                 680                 685

ggc att tac agg ttt gtg act cca gga gaa cgg ccc tcg ggc atg ttc   3911
Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe
        690                 695                 700

gat tcc tcg gtt ctg tgc gag tgc tat gac gcg ggc tgt gct tgg tac   3959
Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr
    705                 710                 715

gag ctc acg ccc gcc gag acc tca gtt agg ttg cgg gct tac cta aac   4007
Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn
720                 725                 730                 735

aca cca ggg ttg ccc gtc tgc cag gac cat ctg gag ttc tgg gag agc   4055
Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser
                740                 745                 750

gtc ttt aca ggc ctc acc cac ata gac gcc cat ttc ttg tcc cag act   4103
Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr
            755                 760                 765

aag cag gca gga gac aac ttc ccc tac ctg gta gca tac cag gct acg   4151
Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr
        770                 775                 780

gtg tgc gcc agg gct cag gct cca cct cca tcg tgg gac caa atg tgg   4199
Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp
    785                 790                 795

aag tgt ctc ata cgg cta aag cct acg ctg cac ggg cca acg ccc ctg   4247
Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu
800                 805                 810                 815

ctg tat agg ctg gga gcc gtt caa aac gag gtt act acc aca cac ccc   4295
Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro
                820                 825                 830

ata acc aaa tac atc atg gca tgc atg tcg gct gac ctg gag gtc gtc   4343
Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val
            835                 840                 845

acg agc acc tgg gtg ctg gta ggc gga gtc cta gca gct ctg gcc gcg   4391
Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala
        850                 855                 860

tat tgc ctg aca aca ggc agc gtg gtc att gtg ggc agg atc atc ttg   4439
Tyr Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
    865                 870                 875

tcc gga aag ccg gcc atc att ccc gac agg gaa gtc ctt tac cgg gag   4487
Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu
880                 885                 890                 895
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ttc gat gag atg gaa gag tgc gcc tca cac ctc cct tac atc gaa cag   4535
Phe Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln
                900                 905                 910

gga atg cag ctc gcc gaa caa ttc aaa cag aag gca atc ggg ttg ctg   4583
Gly Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu
            915                 920                 925

caa aca gcc acc aag caa gcg gag gct gct gct ccc gtg gtg gaa tcc   4631
Gln Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser
        930                 935                 940

aag tgg cgg acc ctc gaa gcc ttc tgg gcg aag cat atg tgg aat ttc   4679
Lys Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe
    945                 950                 955

atc agc ggg ata caa tat tta gca ggc ttg tcc act ctg cct ggc aac   4727
Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn
960                 965                 970                 975

ccc gcg ata gca tca ctg atg gca ttc aca gcc tct atc acc agc ccg   4775
Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro
                980                 985                 990

ctc acc acc caa cat acc ctc ctg ttt aac atc ctg ggg gga tgg gtg   4823
Leu Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val
            995                 1000                1005

gcc gcc caa ctt gct cct ccc agc gct gct tct gct ttc gta ggc gcc   4871
Ala Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala
        1010                1015                1020

ggc atc gct gga gcg gct gtt ggc agc ata ggc ctt ggg aag gtg ctt   4919
Gly Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu
    1025                1030                1035

gtg gat att ttg gca ggt tat gga gca ggg gtg gca ggc gcg ctc gtg   4967
Val Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val
1040                1045                1050                1055

gcc ttt aag gtc atg agc ggc gag atg ccc tcc acc gag gac ctg gtt   5015
Ala Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val
                1060                1065                1070

aac cta ctc cct gct atc ctc tcc cct ggc gcc cta gtc gtc ggg gtc   5063
Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val
            1075                1080                1085

gtg tgc gca gcg ata ctg cgt cgg cac gtg ggc cca ggg gag ggg gct   5111
Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala
        1090                1095                1100

gtg cag tgg atg aac cgg ctg ata gcg ttc gct tcg cgg ggt aac cac   5159
Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His
    1105                1110                1115
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gtc tcc ccc acg cac tat gtg cct gag agc gac gct gca gca cgt gtc   5207
Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val
1120                1125                1130                1135

act cag atc ctc tct agt ctt acc atc act cag ctg ctg aag agg ctt   5255
Thr Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu
                    1140                1145                1150

cac cag tgg atc aac gag gac tgc tcc acg cca tgc tcc ggc tcg tgg   5303
His Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp
            1155                1160                1165

cta aga gat gtt tgg gat tgg ata tgc acg gtg ttg act gat ttc aag   5351
Leu Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys
        1170                1175                1180

acc tgg ctc cag tcc aag ctc ctg ccg cga ttg ccg gga gtc ccc ttc   5399
Thr Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe
    1185                1190                1195

ttc tca tgt caa cgt ggg tac aag gga gtc tgg cgg ggc gac ggc atc   5447
Phe Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile
1200                1205                1210                1215

atg caa acc acc tgc cca tgt gga gca cag atc acc gga cat gtg aaa   5495
Met Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys
                    1220                1225                1230

aac ggt tcc atg agg atc gtg ggg cct agg acc tgt agt aac acg tgg   5543
Asn Gly Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp
            1235                1240                1245

cat gga aca ttc ccc att aac gcg tac acc acg ggc ccc tgc acg ccc   5591
His Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro
        1250                1255                1260

tcc ccg gcg cca aat tat tct agg gcg ctg tgg cgg gtg gct gct gag   5639
Ser Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu
    1265                1270                1275

gag tac gtg gag gtt acg cgg gtg ggg gat ttc cac tac gtg acg ggc   5687
Glu Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly
1280                1285                1290                1295

atg acc act gac aac gta aag tgc ccg tgt cag gtt ccg gcc ccc gaa   5735
Met Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu
                    1300                1305                1310

ttc ttc aca gaa gtg gat ggg gtg cgg ttg cac agg tac gct cca gcg   5783
Phe Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala
            1315                1320                1325

tgc aaa ccc ctc cta cgg gag gag gtc aca ttc ctg gtc ggg ctc aat   5831
Cys Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn
        1330                1335                1340
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caa tac ctg gtt ggg tca cag ctc cca tgc gag ccc gaa ccg gac gta   5879
Gln Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val
    1345                1350                1355

gca gtg ctc act tcc atg ctc acc gac ccc tcc cac att acg gcg gag   5927
Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu
1360                1365                1370                1375

acg gct aag cgt agg ctg gcc agg gga tct ccc ccc tcc ttg gcc agc   5975
Thr Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser
                1380                1385                1390

tca tca gct agc cag ctg tct gcg cct tcc ttg aag gca aca tgc act   6023
Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr
            1395                1400                1405

acc cgt cat gac tcc ccg gac gct gac ctc atc gag gcc aac ctc ctg   6071
Thr Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu
        1410                1415                1420

tgg cgg cag gag atg ggc ggg aac atc acc cgc gtg gag tca gaa aat   6119
Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn
    1425                1430                1435

aag gta gta att ttg gac tct ttc gag ccg ctc caa gcg gag gag gat   6167
Lys Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp
1440                1445                1450                1455

gag agg gaa gta tcc gtt ccg gcg gag atc ctg cgg agg tcc agg aaa   6215
Glu Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys
                1460                1465                1470

ttc cct cga gcg atg ccc ata tgg gca cgc ccg gat tac aac cct cca   6263
Phe Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro
            1475                1480                1485

ctg tta gag tcc tgg aag gac ccg gac tac gtc cct cca gtg gta cac   6311
Leu Leu Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His
        1490                1495                1500

ggg tgt cca ttg ccg cct gcc aag gcc cct ccg ata cca cct cca cgg   6359
Gly Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg
    1505                1510                1515

agg aag agg acg gtt gtc ctg tca gaa tct acc gtg tct tct gcc ttg   6407
Arg Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu
1520                1525                1530                1535

gcg gag ctc gcc aca aag acc ttc ggc agc tcc gaa tcg tcg gcc gtc   6455
Ala Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val
                1540                1545                1550

gac agc ggc acg gca acg gcc tct cct gac cag ccc tcc gac gac ggc   6503
Asp Ser Gly Thr Ala Thr Ala Ser Pro Asp Gln Pro Ser Asp Asp Gly
            1555                1560                1565
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gac gcg gga tcc gac gtt gag tcg tac tcc tcc atg ccc ccc ctt gag   6551
Asp Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu
        1570                1575                1580

ggg gag ccg ggg gat ccc gat ctc agc gac ggg tct tgg tct acc gta   6599
Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val
    1585                1590                1595

agc gag gag gct agt gag gac gtc gtc tgc tgc tcg atg tcc tac aca   6647
Ser Glu Glu Ala Ser Glu Asp Val Val Cys Cys Ser Met Ser Tyr Thr
1600                1605                1610                1615

tgg aca ggc gcc ctg atc acg cca tgc gct gcg gag gaa acc aag ctg   6695
Trp Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu
                1620                1625                1630

ccc atc aat gca ctg agc aac tct ttg ctc cgt cac cac aac ttg gtc   6743
Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val
            1635                1640                1645

tat gct aca aca tct cgc agc gca agc ctg cgg cag aag aag gtc acc   6791
Tyr Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr
        1650                1655                1660

ttt gac aga ctg cag gtc ctg gac gac cac tac cgg gac gtg ctc aag   6839
Phe Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys
    1665                1670                1675

gag atg aag gcg aag gcg tcc aca gtt aag gct aaa ctt cta tcc gtg   6887
Glu Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val
1680                1685                1690                1695

gag gaa gcc tgt aag ctg acg ccc cca cat tcg gcc aga tct aaa ttt   6935
Glu Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe
                1700                1705                1710

ggc tat ggg gca aag gac gtc cgg aac cta tcc agc aag gcc gtt aac   6983
Gly Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn
            1715                1720                1725

cac atc cgc tcc gtg tgg aag gac ttg ctg gaa gac act gag aca cca   7031
His Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro
        1730                1735                1740

att gac acc acc atc atg gca aaa aat gag gtt ttc tgc gtc caa cca   7079
Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro
    1745                1750                1755

gag aag ggg ggc cgc aag cca gct cgc ctt atc gta ttc cca gat ttg   7127
Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu
1760                1765                1770                1775

ggg gtt cgt gtg tgc gag aaa atg gcc ctt tac gat gtg gtc tcc acc   7175
Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr
                1780                1785                1790
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ctc cct cag gcc gtg atg ggc tct tca tac gga ttc caa tac tct cct   7223
Leu Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro
            1795                1800                1805

gga cag cgg gtc gag ttc ctg gtg aat gcc tgg aaa gcg aag aaa tgc   7271
Gly Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys
        1810                1815                1820

cct atg ggc ttc gca tat gac acc cgc tgt ttt gac tca acg gtc act   7319
Pro Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr
    1825                1830                1835

gag aat gac atc cgt gtt gag gag tca atc tac caa tgt tgt gac ttg   7367
Glu Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu
1840                1845                1850                1855

gcc ccc gaa gcc aga cag gcc ata agg tcg ctc aca gag cgg ctt tac   7415
Ala Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr
                1860                1865                1870

atc ggg ggc ccc ctg act aat tct aaa ggg cag aac tgc ggc tat cgc   7463
Ile Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg
            1875                1880                1885

cgg tgc cgc gcg agc ggt gta ctg acg acc agc tgc ggt aat acc ctc   7511
Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu
        1890                1895                1900

aca tgt tac ttg aag gcc gct gcg gcc tgt cga gct gcg aag ctc cag   7559
Thr Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln
    1905                1910                1915

gac tgc acg atg ctc gta tgc gga gac gac ctt gtc gtt atc tgt gaa   7607
Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu
1920                1925                1930                1935

agc gcg ggg acc caa gag gac gag gcg agc cta cgg gcc ttc acg gag   7655
Ser Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu
                1940                1945                1950

gct atg act aga tac tct gcc ccc cct ggg gac ccg ccc aaa cca gaa   7703
Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu
            1955                1960                1965

tac gac ttg gag ttg ata aca tca tgc tcc tcc aat gtg tca gtc gcg   7751
Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala
        1970                1975                1980

cac gat gca tct ggc aaa agg gtg tac tat ctc acc cgt gac ccc acc   7799
His Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr
    1985                1990                1995

acc ccc ctt gcg cgg gct gcg tgg gag aca gct aga cac act cca gtc   7847
Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val
2000                2005                2010                2015
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aat tcc tgg cta ggc aac atc atc atg tat gcg ccc acc ttg tgg gca   7895
Asn Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala
                2020                2025                2030

agg atg atc ctg atg act cat ttc ttc tcc atc ctt cta gct cag gaa   7943
Arg Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu
            2035                2040                2045

caa ctt gaa aaa gcc cta gat tgt cag atc tac ggg gcc tgt tac tcc   7991
Gln Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser
        2050                2055                2060

att gag cca ctt gac cta cct cag atc att caa cga ctc cac ggc ctt   8039
Ile Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu
    2065                2070                2075

agc gca ttt tca ctc cat agt tac tct cca ggt gag atc aat agg gtg   8087
Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val
2080                2085                2090                2095

gct tca tgc ctc agg aaa ctt ggg gta ccg ccc ttg cga gtc tgg aga   8135
Ala Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg
                2100                2105                2110

cat cgg gcc aga agt gtc cgc gct agg cta ctg tcc cag ggg ggg agg   8183
His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg
            2115                2120                2125

gct gcc act tgt ggc aag tac ctc ttc aac tgg gca gta agg acc aag   8231
Ala Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys
        2130                2135                2140

ctc aaa ctc act cca atc ccg gct gcg tcc cag ttg gat tta tcc agc   8279
Leu Lys Leu Thr Pro Ile Pro Ala Ala Ser Gln Leu Asp Leu Ser Ser
    2145                2150                2155

tgg ttc gtt gct ggt tac agc ggg gga gac ata tat cac agc ctg tct   8327
Trp Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser
2160                2165                2170                2175

cgt gcc cga ccc cgc tgg ttc atg tgg tgc cta ctc cta ctt tct gta   8375
Arg Ala Arg Pro Arg Trp Phe Met Trp Cys Leu Leu Leu Leu Ser Val
                2180                2185                2190

ggg gta ggc atc tat cta ctc ccc aac cga tga acggggagct aaacactcca 8428
Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg  *
            2195                2200
ggccaatagg ccatcctgtt tttttccctt tttttttttc tttttttttt tttttttttt 8488
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c atg gac cgg gag atg gca gca tcg tgc gga ggc gcg gtt ttc gta ggt 1849
  Met Asp Arg Glu Met Ala Ala Ser Cys Gly Gly Ala Val Phe Val Gly
   1   5   10   15

ctg ata ctc ttg acc ttg tca ccg cac tat aag ctg ttc ctc gct agg 1897
Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala Arg
            20   25   30

ctc ata tgg tgg tta caa tat ttt atc acc agg gcc gag gca cac ttg 1945
Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His Leu
        35   40   45

caa gtg tgg atc ccc ccc ctc aac gtt cgg ggg ggc cgc gat gcc gtc 1993
Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
    50   55   60

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atc ctc ctc acg tgc gcg atc cac cca gag cta atc ttt acc atc acc   2041
Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile Thr
 65                  70                  75                  80

aaa atc ttg ctc gcc ata ctc ggt cca ctc atg gtg ctc cag gct ggt   2089
Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly
                 85                  90                  95

ata acc aaa gtg ccg tac ttc gtg cgc gca cac ggg ctc att cgt gca   2137
Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg Ala
            100                 105                 110

tgc atg ctg gtg cgg aag gtt gct ggg ggt cat tat gtc caa atg gct   2185
Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala
        115                 120                 125

ctc atg aag ttg gcc gca ctg aca ggt acg tac gtt tat gac cat ctc   2233
Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His Leu
    130                 135                 140

acc cca ctg cgg gac tgg gcc cac gcg ggc cta cga gac ctt gcg gtg   2281
Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala Val
145                 150                 155                 160

gca gtt gag ccc gtc gtc ttc tct gat atg gag acc aag gtt atc acc   2329
Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile Thr
                165                 170                 175

tgg ggg gca gac acc gcg gcg tgt ggg gac atc atc ttg ggc ctg ccc   2377
Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
            180                 185                 190

gtc tcc gcc cgc agg ggg agg gag ata cat ctg gga ccg gca gac agc   2425
Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp Ser
        195                 200                 205

ctt gaa ggg cag ggg tgg cga ctc ctc gcg cct att acg gcc tac tcc   2473
Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser
    210                 215                 220

caa cag acg cga ggc cta ctt ggc tgc atc atc act agc ctc aca ggc   2521
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
225                 230                 235                 240

cgg gac agg aac cag gtc gag ggg gag gtc caa gtg gtc tcc acc gca   2569
Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
                245                 250                 255

aca caa tct ttc ctg gcg acc tgc gtc aat ggc gtg tgt tgg act gtc   2617
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
            260                 265                 270

tat cat ggt gcc ggc tca aag acc ctt gcc ggc cca aag ggc cca atc   2665
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
        275                 280                 285
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acc caa atg tac acc aat gtg gac cag gac ctc gtc ggc tgg caa gcg   2713
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
    290                 295                 300

ccc ccc ggg gcg cgt tcc ttg aca cca tgc acc tgc ggc agc tcg gac   2761
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
305                 310                 315                 320

ctt tac ttg gtc acg agg cat gcc gat gtc att ccg gtg cgc cgg cgg   2809
Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg
                325                 330                 335

ggc gac agc agg ggg agc cta ctc tcc ccc agg ccc gtc tcc tac ttg   2857
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
            340                 345                 350

aag ggc tct tcg ggc ggt cca ctg ctc tgc ccc tcg ggg cac gct gtg   2905
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
        355                 360                 365

ggc atc ttt cgg gct gcc gtg tgc acc cga ggg gtt gcg aag gcg gtg   2953
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
    370                 375                 380

gac ttt gta ccc gtc gag tct atg gaa acc act atg cgg tcc ccg gtc   3001
Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val
385                 390                 395                 400

ttc acg gac aac tcg tcc cct ccg gcc gta ccg cag aca ttc cag gtg   3049
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln Val
                405                 410                 415

gcc cat cta cac gcc cct act ggt agc ggc aag agc act aag gtg ccg   3097
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
            420                 425                 430

gct gcg tat gca gcc caa ggg tat aag gtg ctt gtc ctg aac ccg tcc   3145
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
        435                 440                 445

gtc gcc gcc acc cta ggt ttc ggg gcg tat atg tct aag gca cat ggt   3193
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
    450                 455                 460

atc gac cct aac atc aga acc ggg gta agg acc atc acc acg ggt gcc   3241
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
465                 470                 475                 480

ccc atc acg tac tcc acc tat ggc aag ttt ctt gcc gac ggt ggt tgc   3289
Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
                485                 490                 495

tct ggg ggc gcc tat gac atc ata ata tgt gat gag tgc cac tca act   3337
Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
            500                 505                 510
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gac tcg acc act atc ctg ggc atc ggc aca gtc ctg gac caa gcg gag   3385
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
        515                 520                 525

acg gct gga gcg cga ctc gtc gtg ctc gcc acc gct acg cct ccg gga   3433
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
    530                 535                 540

tcg gtc acc gtg cca cat cca aac atc gag gag gtg gct ctg tcc agc   3481
Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Ser
545                 550                 555                 560

act gga gaa atc ccc ttt tat ggc aaa gcc atc ccc atc gag acc atc   3529
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Thr Ile
                565                 570                 575

aag ggg ggg agg cac ctc att ttc tgc cat tcc aag aag aaa tgt gat   3577
Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp
            580                 585                 590

gag ctc gcc gcg aag ctg tcc ggc ctc gga ctc aat gct gta gca tat   3625
Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Leu Asn Ala Val Ala Tyr
        595                 600                 605

tac cgg ggc ctt gat gta tcc gtc ata cca act agc gga gac gtc att   3673
Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Ile
    610                 615                 620

gtc gta gca acg gac gct cta atg acg ggc ttt acc ggc gat ttc gac   3721
Val Val Ala Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp
625                 630                 635                 640

tca gtg atc gac tgc aat aca tgt gtc acc cag aca gtc gac ttc agc   3769
Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser
                645                 650                 655

ctg gac ccg acc ttc acc att gag acg acg acc gtg cca caa gac gcg   3817
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
            660                 665                 670

gtg tca cgc tcg cag cgg cga ggc agg act ggt agg ggc agg atg ggc   3865
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met Gly
        675                 680                 685

att tac agg ttt gtg act cca gga gaa cgg ccc tcg ggc atg ttc gat   3913
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
    690                 695                 700

tcc tcg gtt ctg tgc gag tgc tat gac gcg ggc tgt gct tgg tac gag   3961
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
705                 710                 715                 720

ctc acg ccc gcc gag acc tca gtt agg ttg cgg gct tac cta aac aca   4009
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
                725                 730                 735
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cca ggg ttg ccc gtc tgc cag gac cat ctg gag ttc tgg gag agc gtc   4057
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val
            740                 745                 750

ttt aca ggc ctc acc cac ata gac gcc cat ttc ttg tcc cag act aag   4105
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
        755                 760                 765

cag gca gga gac aac ttc ccc tac ctg gta gca tac cag gct acg gtg   4153
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
    770                 775                 780

tgc gcc agg gct cag gct cca cct cca tcg tgg gac caa atg tgg aag   4201
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
785                 790                 795                 800

tgt ctc ata cgg cta aag cct acg ctg cac ggg cca acg ccc ctg ctg   4249
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
                805                 810                 815

tat agg ctg gga gcc gtt caa aac gag gtt act acc aca cac ccc ata   4297
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro Ile
            820                 825                 830

acc aaa tac atc atg gca tgc atg tcg gct gac ctg gag gtc gtc acg   4345
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr
        835                 840                 845

agc acc tgg gtg ctg gta ggc gga gtc cta gca gct ctg gcc gcg tat   4393
Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
    850                 855                 860

tgc ctg aca aca ggc agc gtg gtc att gtg ggc agg atc atc ttg tcc   4441
Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
865                 870                 875                 880

gga arg ccg gcc atc att ccc gac agg gaa gtc ctt tac cgg gag ttc   4489
Gly Xaa Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe
                885                 890                 895

gat gag atg gaa gag tgc gcc tca cac ctc cct tac atc gaa cag gga   4537
Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln Gly
            900                 905                 910

atg cag ctc gcc gaa caa ttc aaa cag aag gca atc ggg ttg ctg caa   4585
Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu Gln
        915                 920                 925

aca gcc acc aag caa gcg gag gct gct gct ccc gtg gtg gaa tcc aag   4633
Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys
    930                 935                 940

tgg cgg acc ctc gaa gcc ttc tgg gcg aag cat atg tgg aat ttc atc   4681
Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe Ile
945                 950                 955                 960
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agc ggg ata caa tat tta gca ggc ttg tcc act ctg cct ggc aac ccc   4729
Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro
                965                 970                 975

gcg ata gca tca ctg atg gca ttc aca gcc tct atc acc agc ccg ctc   4777
Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu
            980                 985                 990

acc acc caa cat acc ctc ctg ttt aac atc ctg ggg gga tgg gtg gcc   4825
Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala
        995                1000                1005

gcc caa ctt gct cct ccc agc gct gct tct gct ttc gta ggc gcc ggc   4873
Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly
    1010                1015                1020

atc gct gga gcg gct gtt ggc agc ata ggc ctt ggg aag gtg ctt gtg   4921
Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val
1025                1030                1035                1040

gat att ttg gca ggt tat gga gca ggg gtg gca ggc gcg ctc gtg gcc   4969
Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala
                1045                1050                1055

ttt aag gtc atg agc ggc gag atg ccc tcc acc gag gac ctg gtt aac   5017
Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn
            1060                1065                1070

cta ctc cct gct atc ctc tcc cct ggc gcc cta gtc gtc ggg gtc gtg   5065
Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val
        1075                1080                1085

tgc gca gcg ata ctg cgt cgg cac gtg ggc cca ggg gag ggg gct gtg   5113
Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val
    1090                1095                1100

cag tgg atg aac cgg ctg ata gcg ttc gct tcg cgg ggt aac cac gtc   5161
Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val
1105                1110                1115                1120

tcc ccc acg cac tat gtg cct gag agc gac gct gca gca cgt gtc act   5209
Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr
                1125                1130                1135

cag atc ctc tct agt ctt acc atc act cag ctg ctg aag agg ctt cac   5257
Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His
            1140                1145                1150

cag tgg atc aac gag gac tgc tcc acg cca tgc tcc ggc tcg tgg cta   5305
Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu
        1155                1160                1165

aga gat gtt tgg gat tgg ata tgc acg gtg ttg act gat ttc aag acc   5353
Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys Thr
    1170                1175                1180
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tgg ctc cag tcc aag ctc ctg ccg cga ttg ccg gga gtc ccc ttc ttc   5401
Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe Phe
1185                1190                1195                1200

tca tgt caa cgt ggg tac aag gga gtc tgg cgg ggc gac ggc atc atg   5449
Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met
                1205                1210                1215

caa acc acc tgc cca tgt gga gca cag atc acc gga cat gtg aaa aac   5497
Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn
            1220                1225                1230

tgt tcc atg agg atc gtg ggg cct agg acc tgt agt aac acg tgg cat   5545
Cys Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp His
        1235                1240                1245

gga aca ttc ccc att aac gcg tac acc acg ggc ccc tgc acg ccc tcc   5593
Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser
    1250                1255                1260

ccg gcg cca aat tat tct agg gcg ctg tgg cgg gtg gct gct gag gag   5641
Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu
1265                1270                1275                1280

tac gtg gag gtt acg cgg gtg ggg gat ttc cac tac gtg acg ggc atg   5689
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met
                1285                1290                1295

acc act gac aac gta aag tgc ccg tgt cag gtt ccg gcc ccc gaa ttc   5737
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe
            1300                1305                1310

ttc aca gaa gtg gat ggg gtg cgg ttg cac agg tac gct cca gcg tgc   5785
Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys
        1315                1320                1325

aaa ccc ctc cta cgg gag gag gtc aca ttc ctg gtc ggg ctc aat caa   5833
Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn Gln
    1330                1335                1340

tac ctg gtt ggg tca cag ctc cca tgc gag ccc gaa ccg gac gta gca   5881
Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala
1345                1350                1355                1360

gtg ctc act tcc atg ctc acc gac ccc tcc cac att acg gcg gag acg   5929
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr
                1365                1370                1375

gct aag cgt agg ctg gcc agg gga tct ccc ccc tcc ttg gcc agc tca   5977
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser
            1380                1385                1390

tca gct agc cag ctg tct gcg cct tcc ttg aag gca aca tgc act acc   6025
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr
        1395                1400                1405
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cgt cat gac tcc ccg gac gct gac ctc atc gag gcc aac ctc ctg tgg   6073
Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp
    1410                1415                1420

cgg cag gag atg ggc ggg aac atc acc cgc gtg gag tca gaa aat aag   6121
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys
1425                1430                1435                1440

gta gta att ttg gac tct ttc gag ccg ctc caa gcg gag gag gat gag   6169
Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp Glu
                1445                1450                1455

agg gaa gta tcc gtt ccg gcg gag atc ctg cgg agg tcc agg aaa ttc   6217
Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys Phe
            1460                1465                1470

cct cga gcg atg ccc ata tgg gca cgc ccg gat tac aac cct cca ctg   6265
Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu
        1475                1480                1485

ttr gag tcc tgg aag gac ccg gac tac gtc cct cca gtg gta cac ggg   6313
Xaa Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His Gly
    1490                1495                1500

tgt cca ttg ccg cct gcc aag gcc cct ccg ata cca cct cca cgg agg   6361
Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg Arg
1505                1510                1515                1520

aag agg acg gtt gtc ctg tca gaa tct acc gtg tct tct gcc ttg gcg   6409
Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu Ala
                1525                1530                1535

gag ctc gcc aca aag acc ttc ggc agc tcc gaa tcg tcg gcc gtc gac   6457
Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val Asp
            1540                1545                1550

agc ggc acg gca acg gcc tct cct gac cag ccc tcc gac gac ggc gac   6505
Ser Gly Thr Ala Thr Ala Ser Pro Asp Gln Pro Ser Asp Asp Gly Asp
        1555                1560                1565

gcg gga tcc gac gtt gag tcg tac tcc tcc atg ccc ccc ctt gag ggg   6553
Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly
    1570                1575                1580

gag ccg ggg gat ccc gat ctc agc gac ggg tct tgg tct acc gta agc   6601
Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser
1585                1590                1595                1600

gag gag gct agt gag gac gtc gtc tgc tgc tcg atg tcc tac aca tgg   6649
Glu Glu Ala Ser Glu Asp Val Val Cys Cys Ser Met Ser Tyr Thr Trp
                1605                1610                1615
aca ggc gcc ctg atc acg cca tgc gct gcg gag gaa acc aag ctg ccc   6697
Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu Pro
            1620                1625                1630

atc aat gca ctg agc aac tct ttg ctc cgt cac cac aac ttg gtc tat   6745
Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr
        1635                1640                1645
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gct aca aca tct cgc agc gca agc ctg cgg cag aag aag gtc acc ttt   6793
Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr Phe
    1650                1655                1660

gac aga ctg cag gtc ctg gac gac cac tac cgg gac gtg ctc aag gag   6841
Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys Glu
1665                1670                1675                1680

atg aag gcg aag gcg tcc aca gtt aag gct aaa ctt cta tcc gtg gag   6889
Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val Glu
                1685                1690                1695

gaa gcc tgt aag ctg acg ccc cca cat tcg gcc aga tct aaa ttt ggc   6937
Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe Gly
            1700                1705                1710

tat ggg gca aag gac gtc cgg aac cta tcc agc aag gcc gtt aac cac   6985
Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
        1715                1720                1725

atc cgc tcc gtg tgg aag gac ttg ctg gaa gac act gag aca cca att   7033
Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro Ile
    1730                1735                1740

gac acc acc atc atg gca aaa aat gag gtt ttc tgc gtc caa cca gag   7081
Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu
1745                1750                1755                1760

aag ggg ggc cgc aag cca gct cgc ctt atc gta ttc cca gat ttg ggg   7129
Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly
                1765                1770                1775

gtt cgt gtg tgc gag aaa atg gcc ctt tac gat gtg gtc tcc acc ctc   7177
Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr Leu
            1780                1785                1790

cct cag gcc gtg atg ggc tct tca tac gga ttc caa tac tct cct gga   7225
Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly
        1795                1800                1805

cag cgg gtc gag ttc ctg gtg aat gcc tgg aaa gcg aag aaa tgc cct   7273
Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys Pro
    1810                1815                1820

atg ggc ttc gca tat gac acc cgc tgt ttt gac tca acg gtc act gag   7321
Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
1825                1830                1835                1840

aat gac atc cgt gtt gag gag tca atc tac caa tgt tgt gac ttg gcc   7369
Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu Ala
                1845                1850                1855

ccc gaa gcc aga cag gcc ata agg tcg ctc aca gag cgg ctt tac atc   7417
Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr Ile
            1860                1865                1870
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ggg ggc ccc ctg act aat tct aaa ggg cag aac tgc ggc tat cgc cgg   7465
Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg Arg
        1875                1880                1885

tgc cgc gcg agc ggt gta ctg acg acc agc tgc ggt aat acc ctc aca   7513
Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr
    1890                1895                1900

tgt tac ttg aag gcc gct gcg gcc tgt cga gct gcg aag ctc cag gac   7561
Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln Asp
1905                1910                1915                1920

tgc acg atg ctc gta tgc gga gac gac ctt gtc gtt atc tgt gaa agc   7609
Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser
                1925                1930                1935

gcg ggg acc caa gag gac gag gcg agc cta cgg gcc ttc acg gag gct   7657
Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu Ala
            1940                1945                1950

atg act aga tac tct gcc ccc cct ggg gac ccg ccc aaa cca gaa tac   7705
Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu Tyr
        1955                1960                1965

gac ttg gag ttg ata aca tca tgc tcc tcc aat gtg tca gtc gcg cac   7753
Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His
    1970                1975                1980

gat gca tct ggc aaa agg gtg tac tat ctc acc cgt gac ccc acc acc   7801
Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
1985                1990                1995                2000

ccc ctt gcg cgg gct gcg tgg gag aca gct aga cac act cca gtc aat   7849
Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn
                2005                2010                2015

tcc tgg cta ggc aac atc atc atg tat gcg ccc acc ttg tgg gca agg   7897
Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg
            2020                2025                2030

atg atc ctg atg act cat ttc ttc tcc atc ctt cta gct cag gaa caa   7945
Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln
        2035                2040                2045

ctt gaa aaa gcc cta gat tgt cag atc tac ggg gcc tgt tac tcc att   7993
Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile
    2050                2055                2060

gag cca ctt gac cta cct cag atc att caa cga ctc cac ggc ctt agc   8041
Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu Ser
2065                2070                2075                2080

gca ttt tca ctc cat agt tac tct cca ggt gag atc aat agg gtg gct   8089
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
                2085                2090                2095
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tca tgc ctc agg aaa ctt ggg gta ccg ccc ttg cga gtc tgg aga cat   8137
Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg His
            2100                2105                2110

cgg gcc aga agt gtc cgc gct agg cta ctg tcc cag ggg ggg agg gct   8185
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg Ala
        2115                2120                2125

gcc act tgt ggc aag tac ctc ttc aac tgg gca gta agg acc aag ctc   8233
Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
    2130                2135                2140

aaa ctc act cca atc ccg gct gcg tcc cag ttg gat tta tcc agc tgg   8281
Lys Leu Thr Pro Ile Pro Ala Ala Ser Gln Leu Asp Leu Ser Ser Trp
2145                2150                2155                2160

ttc gtt gct ggt tac agc ggg gga gac ata tat cac agc ctg tct cgt   8329
Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser Arg
                2165                2170                2175

gcc cga ccc cgc tgg ttc atg tgg tgc cta ctc cta ctt tct gta ggg   8377
Ala Arg Pro Arg Trp Phe Met Trp Cys Leu Leu Leu Leu Ser Val Gly
            2180                2185                2190

gta ggc atc tat cta ctc ccc aac cga tga acggggagct aaacactcca     8427
Val Gly Ile Tyr Leu Leu Pro Asn Arg  *
        2195                2200

ggccaatagg ccatcctgtt tttttccccc tttttttttt tttttttttc tttttttttt 8487
tttttttttt tttttttttc tccttttttt tcctcttttt ttccttttct ttcctttggt 8547
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gagagtgctg atactggcct ctctgcagat caagt                            8642

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<212> PRT
<213> HCV

<220>
<221> VARIANT
<222> 882
<223> Xaa is Lys or Arg

<221> VARIANT
<222> 1489
<223> Xaa is Leu

<400> 3
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 1                5                  10                  15
Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala Arg
            20                  25                  30
Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His Leu
        35                  40                  45
Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
    50                  55                  60
Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile Thr
65                  70                  75                  80
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Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly
                85                  90                  95
Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg Ala
            100                 105                 110
Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala
        115                 120                 125
Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His Leu
    130                 135                 140
Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala Val
145                 150                 155                 160
Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile Thr
                165                 170                 175
Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
            180                 185                 190
Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp Ser
        195                 200                 205
Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser
    210                 215                 220
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
225                 230                 235                 240
Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
                245                 250                 255
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
            260                 265                 270
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
        275                 280                 285
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
    290                 295                 300
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
305                 310                 315                 320
Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg
                325                 330                 335
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
            340                 345                 350
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
        355                 360                 365
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
    370                 375                 380
Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val
385                 390                 395                 400
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln Val
                405                 410                 415
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
            420                 425                 430
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
        435                 440                 445
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
    450                 455                 460
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
465                 470                 475                 480
Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
                485                 490                 495
Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
            500                 505                 510
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
        515                 520                 525
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
    530                 535                 540
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Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Ser
545 550 555 560
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Thr Ile
565 570 575
Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp
580 585 590
Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Leu Asn Ala Val Ala Tyr
595 600 605
Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Ile
610 615 620
Val Val Ala Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp
625 630 635 640
Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser
645 650 655
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
660 665 670
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met Gly
675 680 685
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
690 695 700
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
705 710 715 720
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
725 730 735
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val
740 745 750
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
755 760 765
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
770 775 780
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
785 790 795 800
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
805 810 815
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro Ile
820 825 830
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr
835 840 845
Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
850 855 860
Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
865 870 875 880
Gly Xaa Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe
885 890 895
Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln Gly
900 905 910
Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu Gln
915 920 925
Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys
930 935 940
Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe Ile
945 950 955 960
Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro
965 970 975
Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu
980 985 990
Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala
995 1000 1005

Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly
1010 1015 1020
Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val
1025 1030 1035 1040
Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala
1045 1050 1055
Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn
1060 1065 1070
Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val
1075 1080 1085
Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val
1090 1095 1100
Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val
1105 1110 1115 1120
Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr
1125 1130 1135
Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His
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Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu
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Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys Thr
1170 1175 1180
Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe Phe
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Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met
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Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn
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Cys Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp His
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Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser
1250 1255 1260
Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu
1265 1270 1275 1280
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met
1285 1290 1295
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe
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Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys
1315 1320 1325
Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn Gln
1330 1335 1340
Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala
1345 1350 1355 1360
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr
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Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser
1380 1385 1390
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr
1395 1400 1405
Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp
1410 1415 1420
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys
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Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp Glu
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Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys Phe
1460 1465 1470

Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu
1475 1480 1485
Xaa Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His Gly
1490 1495 1500
Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg Arg
1505 1510 1515 1520
Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu Ala
1525 1530 1535
Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val Asp
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Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly
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Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser
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Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu Pro
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Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr
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Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr Phe
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Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys Glu
1665 1670 1675 1680
Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val Glu
1685 1690 1695
Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe Gly
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Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
1715 1720 1725
Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro Ile
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Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu
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Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly
1765 1770 1775
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Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly
1795 1800 1805
Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys Pro
1810 1815 1820
Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
1825 1830 1835 1840
Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu Ala
1845 1850 1855
Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr Ile
1860 1865 1870
Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg Arg
1875 1880 1885
Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr
1890 1895 1900
Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln Asp
1905 1910 1915 1920
Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser
1925 1930 1935

Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu Ala
1940 1945 1950
Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu Tyr
1955 1960 1965
Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His
1970 1975 1980
Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
1985 1990 1995 2000
Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn
2005 2010 2015
Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg
2020 2025 2030
Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln
2035 2040 2045
Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile
2050 2055 2060
Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu Ser
2065 2070 2075 2080
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
2085 2090 2095
Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg His
2100 2105 2110
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg Ala
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c atg gac cgg gag atg gca gca tcg tgc gga ggc gcg gtt ttc gta ggt 1849
  Met Asp Arg Glu Met Ala Ala Ser Cys Gly Gly Ala Val Phe Val Gly
   1               5                  10                  15

ctg ata ctc ttg acc ttg tca ccg cac tat aag ctg ttc ctc gct agg   1897
Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala Arg
            20                  25                  30

ctc ata tgg tgg tta caa tat ttt atc acc agg gcc gag gca cac ttg   1945
Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His Leu
        35                  40                  45

caa gtg tgg atc ccc ccc ctc aac gtt cgg ggg ggc cgc gat gcc gtc   1993
Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
    50                  55                  60

atc ctc ctc acg tgc gcg atc cac cca gag cta atc ttt acc atc acc   2041
Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile Thr
65                  70                  75                  80

aaa atc ttg ctc gcc ata ctc ggt cca ctc atg gtg ctc cag gct ggt   2089
Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly
                85                  90                  95

ata acc aaa gtg ccg tac ttc gtg cgc gca cac ggg ctc att cgt gca   2137
Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg Ala
            100                 105                 110

tgc atg ctg gtg cgg aag gtt gct ggg ggt cat tat gtc caa atg gct   2185
Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala
        115                 120                 125

ctc atg aag ttg gcc gca ctg aca ggt acg tac gtt tat gac cat ctc   2233
Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His Leu
    130                 135                 140

acc cca ctg cgg gac tgg gcc cac gcg ggc cta cga gac ctt gcg gtg   2281
Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala Val
145                 150                 155                 160
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gca gtt gag ccc gtc gtc ttc tct gat atg gag acc aag gtt atc acc   2329
Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile Thr
                165                 170                 175

tgg ggg gca gac acc gcg gcg tgt ggg gac atc atc ttg ggc ctg ccc   2377
Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
            180                 185                 190

gtc tcc gcc cgc agg ggg agg gag ata cat ctg gga ccg gca gac agc   2425
Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp Ser
        195                 200                 205

ctt gaa ggg cag ggg tgg cga ctc ctc gcg cct att acg gcc tac tcc   2473
Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser
    210                 215                 220

caa cag acg cga ggc cta ctt ggc tgc atc atc act agc ctc aca ggc   2521
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
225                 230                 235                 240

cgg gac agg aac cag gtc gag ggg gag gtc caa gtg gtc tcc acc gca   2569
Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
                245                 250                 255

aca caa tct ttc ctg gcg acc tgc gtc aat ggc gtg tgt tgg act gtc   2617
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
            260                 265                 270

tat cat ggt gcc ggc tca aag acc ctt gcc ggc cca aag ggc cca atc   2665
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
        275                 280                 285

acc caa atg tac acc aat gtg gac cag gac ctc gtc ggc tgg caa gcg   2713
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
    290                 295                 300

ccc ccc ggg gcg cgt tcc ttg aca cca tgc acc tgc ggc agc tcg gac   2761
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
305                 310                 315                 320

ctt tac ttg gtc acg aag cat gcc gat gtc att ccg gtg cgc cgg cgg   2809
Leu Tyr Leu Val Thr Lys His Ala Asp Val Ile Pro Val Arg Arg Arg
                325                 330                 335

ggc gac agc agg ggg agc cta ctc tcc ccc cgg ccc gtc tcc tac ttg   2857
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
            340                 345                 350

aag ggc tct tcg ggc ggt cca ctg ctc tgc ccc tcg ggg cac gct gtg   2905
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
        355                 360                 365

ggc atc ttt cgg gct gcc gtg tgc acc cga ggg gtt gcg aag gcg gtg   2953
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
    370                 375                 380
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gac ttt gta ccc gtc gag tct atg gaa acc act atg cgg tcc ccg gtc   3001
Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val
385                 390                 395                 400

ttc acg gac aac tcg tcc cct ccg gcc gta ccg cag aca ttc cag gtg   3049
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln Val
                405                 410                 415

gcc cat cta cac gcc cct act ggt agc ggc aag agc act aag gtg ccg   3097
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
            420                 425                 430

gct gcg tat gca gcc caa ggg tat aag gtg ctt gtc ctg aac ccg tcc   3145
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
        435                 440                 445

gtc gcc gcc acc cta ggt ttc ggg gcg tat atg tct aag gca cat ggt   3193
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
    450                 455                 460

atc gac cct aac atc aga acc ggg gta agg acc atc acc acg ggt gcc   3241
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
465                 470                 475                 480

ccc atc acg tac tcc acc tat ggc aag ttt ctt gcc gac ggt ggt tgc   3289
Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
                485                 490                 495

tct ggg ggc gcc tat gac atc ata ata tgt gat gag tgc cac tca act   3337
Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
            500                 505                 510

gac tcg acc act atc ctg ggc atc ggc aca gtc ctg gac caa gcg gag   3385
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
        515                 520                 525

acg gct gga gcg cga ctc gtc gtg ctc gcc acc gct acg cct ccg gga   3433
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
    530                 535                 540

tcg gtc acc gtg cca cat cca aac atc gag gag gtg gct ctg tcc agc   3481
Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Ser
545                 550                 555                 560

act gga gaa atc ccc ttt tat ggc aaa gcc atc ccc atc gag acc atc   3529
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Thr Ile
                565                 570                 575

aag ggg ggg agg cac ctc att ttc tgc cat tcc aag aag aaa tgt gat   3577
Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp
            580                 585                 590

gag ctc gcc gcg aag ctg tcc ggc ctc gga ctc aat gct gta gca tat   3625
Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Leu Asn Ala Val Ala Tyr
        595                 600                 605
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tac cgg ggc ctt gat gta tcc gtc ata cca act agc gga gac gtc att   3673
Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Ile
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gtc gta gca acg gac gct cta atg acg ggc ttt acc ggc gat ttc gac   3721
Val Val Ala Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp
625                 630                 635                 640

tca gtg atc gac tgc aat aca tgt gtc acc cag aca gtc gac ttc agc   3769
Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser
                645                 650                 655

ctg gac ccg acc ttc acc att gag acg acg acc gtg cca caa gac gcg   3817
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
            660                 665                 670

gtg tca cgc tcg cag cgg cga ggc agg act ggt agg ggc agg atg ggc   3865
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met Gly
        675                 680                 685

att tac agg ttt gtg act cca gga gaa cgg ccc tcg ggc atg ttc gat   3913
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
    690                 695                 700

tcc tcg gtt ctg tgc gag tgc tat gac gcg ggc tgt gct tgg tac gag   3961
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
705                 710                 715                 720

ctc acg ccc gcc gag acc tca gtt agg ttg cgg gct tac cta aac aca   4009
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
                725                 730                 735

cca ggg ttg ccc gtc tgc cag gac cat ctg gag ttc tgg gag ggc gtc   4057
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly Val
            740                 745                 750

ttt aca ggc ctc acc cac ata gac gcc cat ttc ttg tcc cag act aag   4105
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
        755                 760                 765

cag gca gga gac aac ttc ccc tac ctg gta gca tac cag gct acg gtg   4153
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
    770                 775                 780

tgc gcc agg gct cag gct cca cct cca tcg tgg gac caa atg tgg aag   4201
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
785                 790                 795                 800

tgt ctc ata cgg cta aag cct acg ctg cac ggg cca acg ccc ctg ctg   4249
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
                805                 810                 815

tat agg ctg gga gcc gtt caa aac gag gtt act acc aca cac ccc ata   4297
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro Ile
            820                 825                 830
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acc aaa tac atc atg gca tgc atg tcg gct gac ctg gag gtc gtc acg   4345
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr
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agc acc tgg gtg ctg gta ggc gga gtc cta gca gct ctg gcc gcg tat   4393
Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
    850                 855                 860

tgc ctg aca aca ggc agc gtg gtc att gtg ggc agg atc atc ttg tcc   4441
Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
865                 870                 875                 880

gga agg ccg gcc atc att ccc gac agg gaa gtc ctt tac cgg gag ttc   4489
Gly Arg Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe
                885                 890                 895

gat gag atg gaa gag tgc gcc tca cac ctc cct tac atc gaa cag gga   4537
Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln Gly
            900                 905                 910

atg cag ctc gcc gaa caa ttc aaa cag aag gca atc ggg ttg ctg caa   4585
Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu Gln
        915                 920                 925

aca gcc acc aag caa gcg gag gct gct gct ccc gtg gtg gaa tcc aag   4633
Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys
    930                 935                 940

tgg cgg acc ctc gaa gcc ttc tgg gcg aag cat atg tgg aat ttc atc   4681
Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe Ile
945                 950                 955                 960

agc ggg ata caa tat tta gca ggc ttg tcc act ctg cct ggc aac ccc   4729
Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro
                965                 970                 975

gcg ata gca tca ctg atg gca ttc aca gcc tct atc acc agc ccg ctc   4777
Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu
            980                 985                 990

acc acc caa cat acc ctc ctg ttt aac atc ctg ggg gga tgg gtg gcc   4825
Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala
        995                 1000                1005

gcc caa ctt gct cct ccc agc gct gct tcc gct ttc gta ggc gcc ggc   4873
Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly
    1010                1015                1020

atc gct gga gcg gct gtt ggc agc ata ggc ctt ggg aag gtg ctt gtg   4921
Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val
1025                1030                1035                1040

gat att ttg gca ggt tat gga gca ggg gtg gca ggc gcg ctc gtg gcc   4969
Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala
                1045                1050                1055
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ttt aag gtc atg agc ggc gag atg ccc tcc acc gag gac ctg gtt aac   5017
Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn
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cta ctc cct gct atc ctc tcc cct ggc gcc cta gtc gtc ggg gtc gtg   5065
Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val
        1075                1080                1085

tgc gca gcg ata ctg cgt cgg cac gtg ggc cca ggg gag ggg gct gtg   5113
Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val
    1090                1095                1100

cag tgg atg aac cgg ctg ata gcg ttc gct tcg cgg ggt aac cac gtc   5161
Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val
1105                1110                1115                1120

tcc ccc acg cac tat gtg cct gag agc gac gct gca gca cgt gtc act   5209
Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr
                1125                1130                1135

cag atc ctc tct agt ctt acc atc act cag ctg ctg aag agg ctt cac   5257
Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His
            1140                1145                1150

cag tgg atc aac gag gac tgc tcc acg cca tgc tcc ggc tcg tgg cta   5305
Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu
        1155                1160                1165

aga gat gtt tgg gat tgg ata tgc acg gtg ttg act gat ttc aag gcc   5353
Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys Ala
    1170                1175                1180

tgg ctc cag tcc aag ctc ctg ccg cga ttg ccg gga gtc ccc ttc ttc   5401
Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe Phe
1185                1190                1195                1200

tca tgt caa cgt ggg tac aag gga gtc tgg cgg ggc gac ggc atc atg   5449
Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met
                1205                1210                1215

caa acc acc tgc cca tgt gga gca cag atc acc gga cat gtg aaa aac   5497
Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn
            1220                1225                1230

tgt tcc atg agg atc gtg ggg cct agg acc tgt agt aac acg tgg cat   5545
Cys Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp His
        1235                1240                1245

gga aca ttc ccc att aac gcg tac acc acg ggc ccc tgc acg ccc tcc   5593
Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser
    1250                1255                1260

ccg gcg cca aat tat tct agg gcg ctg tgg cgg gtg gct gct gag gag   5641
Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu
1265                1270                1275                1280
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tac gtg gag gtt acg cga gtg ggg gat ttc cac tac gtg acg ggc atg   5689
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met
                1285                1290                1295

acc act gac aac gta aag tgc ccg tgt cag gtt ccg gcc ccc gaa ttc   5737
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe
            1300                1305                1310

ttc aca gaa gtg gat ggg gtg cgg ttg cac agg tac gct cca gcg tgc   5785
Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys
        1315                1320                1325

aaa ccc ctc cta cgg gag gag gtc aca ttc ctg gtc ggg ctc aat caa   5833
Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn Gln
    1330                1335                1340

tac ctg gtt ggg tca cag ctc cca tgc gag ccc gaa ctg gac gta gca   5881
Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Leu Asp Val Ala
1345                1350                1355                1360

gtg ctc act tcc atg ctc acc gac ccc tcc cac att acg gcg gag acg   5929
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr
                1365                1370                1375

gct aag cgt agg ctg gcc agg gga tct ccc ccc tcc ttg gcc agc tca   5977
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser
            1380                1385                1390

tca gct agc cag ctg tct gcg cct tcc ttg aag gca aca tgc act acc   6025
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr
        1395                1400                1405

cgt cat gac tcc ccg gac gct gac ctc atc gag gcc aac ctc ctg tgg   6073
Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp
    1410                1415                1420

cgg cag gag atg ggc ggg aac atc acc cgc gtg gag tca gaa aat aag   6121
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys
1425                1430                1435                1440

gta gta att ttg gac tct ttc gag ccg ctc caa gcg gag gag gat gag   6169
Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp Glu
                1445                1450                1455

agg gaa gta tcc gtt ccg gcg gag atc ctg cgg agg tcc agg aaa ttc   6217
Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys Phe
            1460                1465                1470

cct cga gcg atg ccc ata tgg gca cgc ccg gat tac aac cct cca ctg   6265
Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu
        1475                1480                1485

ttg gag tcc tgg aag gac ccg gac tac gtc cct cca gtg gta cac ggg   6313
Leu Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His Gly
    1490                1495                1500
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tgt cca ttg ccg cct gcc aag gcc cct ccg ata cca cct cca cgg agg   6361
Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg Arg
1505                 1510                 1515                 1520

aag agg acg gtt gtc ctg tca gaa tct acc gtg tct tct gcc ttg gcg   6409
Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu Ala
                1525                 1530                 1535

gag ctc gcc aca aag acc ttc ggc agc tcc gaa tcg tcg gcc gtc gac   6457
Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val Asp
            1540                 1545                 1550

agc ggc acg gca acg gcc tct cct gac cag ccc tcc gac gac ggc gac   6505
Ser Gly Thr Ala Thr Ala Ser Pro Asp Gln Pro Ser Asp Asp Gly Asp
        1555                 1560                 1565

gcg gga tcc gac gtt gag tcg tac tcc tcc atg ccc ccc ctt gag ggg   6553
Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly
    1570                 1575                 1580

gag ccg ggg gat ccc gat ctc agc gac ggg tct tgg tct acc gta agc   6601
Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser
1585                 1590                 1595                 1600

gag gag gct agt gag gac gtc gtc tgc tgc tcg atg tcc tac aca tgg   6649
Glu Glu Ala Ser Glu Asp Val Val Cys Cys Ser Met Ser Tyr Thr Trp
                1605                 1610                 1615

acg ggc gcc ctg atc acg cca tgc gct gcg gag gaa acc aag ctg ccc   6697
Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu Pro
            1620                 1625                 1630

atc aat gca ctg agc aac tct ttg ctc cgt cac cac aac ttg gtc tat   6745
Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr
        1635                 1640                 1645

gct aca aca tct cgc agc gca agc ctg cgg cag aag aag gtc acc ttt   6793
Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr Phe
    1650                 1655                 1660

gac aga ctg cag gtc ctg gac gac cac tac cgg gac gtg ctc aag gag   6841
Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys Glu
1665                 1670                 1675                 1680

atg aag gcg aag gcg tcc aca gtt aag gct aaa ctt cta tcc gtg gag   6889
Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val Glu
                1685                 1690                 1695

gaa gcc tgt aag ctg acg ccc cca cat tcg gcc aga tct aaa ttt ggc   6937
Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe Gly
            1700                 1705                 1710

tat ggg gca aag gac gtc cgg aac cta tcc agc aag gcc gtt aac cac   6985
Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
        1715                 1720                 1725
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atc cgc tcc gtg tgg aag gac ttg ctg gaa gac act gag aca cca att   7033
Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro Ile
    1730                1735                1740

gac acc acc atc atg gca aaa aat gag gtt ttc tgc gtc caa cca gag   7081
Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu
1745                1750                1755                1760

aag ggg ggc cgc aag cca gct cgc ctt atc gta ttc cca gat ttg ggg   7129
Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly
                1765                1770                1775

gtt cgt gtg tgc gag aaa atg gcc ctt tac gat gtg gtc tcc acc ctc   7177
Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr Leu
            1780                1785                1790

cct cag gcc gtg atg ggc tct tca tac gga ttc caa tac tct cct gga   7225
Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly
        1795                1800                1805

cag cgg gtc gag ttc ctg gtg aat gcc tgg aaa gcg aag aaa tgc cct   7273
Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys Pro
    1810                1815                1820

atg ggc ttc gca tat gac acc cgc tgt ttt gac tca acg gtc act gag   7321
Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
1825                1830                1835                1840

aat gac atc cgt gtt gag gag tca atc tac caa tgt tgt gac ttg gcc   7369
Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu Ala
                1845                1850                1855

ccc gaa gcc aga cag gcc ata agg tcg ctc aca gag cgg ctt tac atc   7417
Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr Ile
            1860                1865                1870

ggg ggc ccc ctg act aat tct aaa ggg cag aac tgc ggc tat cgc cgg   7465
Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg Arg
        1875                1880                1885

tgc cgc gcg agc ggt gta ctg acg acc agc tgc ggt aat acc ctc aca   7513
Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr
    1890                1895                1900

tgt tac ttg aag gcc gct gcg gcc tgt cga gct gcg aag ctc cag gac   7561
Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln Asp
1905                1910                1915                1920

tgc acg atg ctc gta tgc gga gac gac ctt gtc gtt atc tgt gaa agc   7609
Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser
                1925                1930                1935

gcg ggg acc caa gag gac gag gcg agc cta cgg gcc ttc acg gag gct   7657
Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu Ala
            1940                1945                1950
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atg act aga tac tct gcc ccc cct ggg gac ccg ccc aaa cca gaa tac   7705
Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu Tyr
        1955                1960                1965

gac ttg gag ttg ata aca tca tgc tcc tcc aat gtg tca gtc gcg cac   7753
Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His
    1970                1975                1980

gat gca tct ggc aaa agg gtg tac tat ctc acc cgt gac ccc acc acc   7801
Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
1985                1990                1995                2000

ccc ctt gcg cgg gct gcg tgg gag aca gct aga cac act cca gtc aat   7849
Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn
                2005                2010                2015

tcc tgg cta ggc aac atc atc atg tat gcg ccc acc ttg tgg gca agg   7897
Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg
            2020                2025                2030

atg atc ctg atg act cat ttc ttc tcc atc ctt cta gct cag gaa caa   7945
Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln
        2035                2040                2045

ctt gaa aaa gcc cta gat tgt cag atc tac ggg gcc tgt tac tcc att   7993
Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile
    2050                2055                2060

gag cca ctt gac cta cct cag atc att caa cga ctc cac ggc ctt agc   8041
Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu Ser
2065                2070                2075                2080

gca ttt tca ctc cat agt tac tct cca ggt gag atc aat agg gtg gct   8089
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
                2085                2090                2095

tca tgc ctc agg aaa ctt ggg gta ccg ccc ttg cga gtc tgg aga cat   8137
Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg His
            2100                2105                2110

cgg gcc aga agt gtc cgc gct agg cta ctg tcc cag ggg ggg agg gct   8185
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg Ala
        2115                2120                2125

gcc act tgt ggc aag tac ctc ttc aac tgg gca gta agg acc aag ctc   8233
Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
    2130                2135                2140

aaa ctc act cca atc ccg gct gcg tcc cag ttg gat tta tcc agc tgg   8281
Lys Leu Thr Pro Ile Pro Ala Ala Ser Gln Leu Asp Leu Ser Ser Trp
2145                2150                2155                2160

ttc gtt gct ggt tac agc ggg gga gac ata tat cac agc ctg tct cgt   8329
Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser Arg
                2165                2170                2175
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gcc cga ccc cgc tgg ttc atg tgg tgc cta ctc cta ctt tct gta ggg   8377
Ala Arg Pro Arg Trp Phe Met Trp Cys Leu Leu Leu Leu Ser Val Gly
            2180                2185                2190

gta ggc atc tat cta ctc ccc aac cga tga acggggagct aaacactcca     8427
Val Gly Ile Tyr Leu Leu Pro Asn Arg  *
        2195                2200

ggccaatagg ccatcctgtt ttttcccttt ttttttttt ttttttttt ttttttttt 8487
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c atg gac cgg gag atg gca gca tcg tgc gga ggc gcg gtt ttc gta ggt 1849
  Met Asp Arg Glu Met Ala Ala Ser Cys Gly Gly Ala Val Phe Val Gly
   1               5                  10                  15
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ctg ata ctc ttg acc ttg tca ccg cac tat aag ctg ttc ctc gct agg   1897
Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala Arg
                20                  25                  30

ctc ata tgg tgg tta caa tat ttt atc acc agg gcc gag gca cac ttg   1945
Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His Leu
            35                  40                  45

caa gtg tgg atc ccc ccc ctc aac gtt cgg ggg ggc cgc gat gcc gtc   1993
Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
        50                  55                  60

atc ctc ctc acg tgc gcg atc cac cca gag cta atc ttt acc atc acc   2041
Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile Thr
65                  70                  75                  80

aaa atc ttg ctc gcc ata ctc ggt cca ctc atg gtg ctc cag gct ggt   2089
Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly
                85                  90                  95

ata acc aaa gtg ccg tac ttc gtg cgc gca cac ggg ctc att cgt gca   2137
Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg Ala
            100                 105                 110

tgc atg ctg gtg cgg aag gtt gct ggg ggt cat tat gtc caa atg gct   2185
Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala
        115                 120                 125

ctc atg aag ttg gcc gca ctg aca ggt acg tac gtt tat gac cat ctc   2233
Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His Leu
    130                 135                 140

acc cca ctg cgg gac tgg gcc cac gcg ggc cta cga gac ctt gcg gtg   2281
Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala Val
145                 150                 155                 160

gca gtt gag ccc gtc gtc ttc tct gat atg gag acc aag gtt atc acc   2329
Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile Thr
                165                 170                 175

tgg ggg gca gac acc gcg gcg tgt ggg gac atc atc ttg ggc ctg ccc   2377
Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
            180                 185                 190

gtc tcc gcc cgc agg ggg agg gag ata cat ctg gga ccg gca gac agc   2425
Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp Ser
        195                 200                 205

ctt gaa ggg cag ggg tgg cga ctc ctc gcg cct att acg gcc tac tcc   2473
Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser
    210                 215                 220

caa cag acg cga ggc cta ctt ggc tgc atc atc act agc ctc aca ggc   2521
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
225                 230                 235                 240
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cgg gac agg aac cag gtc gag ggg gag gtc caa gtg gtc tcc acc gca   2569
Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
                245                 250                 255

aca caa tct ttc ctg gcg acc tgc gtc aat ggc gtg tgt tgg act gtc   2617
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
            260                 265                 270

tat cat ggt gcc ggc tca aag acc ctt gcc ggc cca aag ggc cca atc   2665
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
        275                 280                 285

acc caa atg tac acc aat gtg gac cag gac ctc gtc ggc tgg caa gcg   2713
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
    290                 295                 300

ccc ccc ggg gcg cgt tcc ttg aca cca tgc acc tgc ggc agc tcg gac   2761
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
305                 310                 315                 320

ctt tac ttg gtc acg agg cat gcc gat gtc att ccg gtg cgc cgg cgg   2809
Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg
                325                 330                 335

ggc gac agc agg ggg agc cta ctc tcc ccc agg ccc gtc tcc tac ttg   2857
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
            340                 345                 350

aag ggc tct tcg ggc ggt cca ctg ctc tgc ccc tcg ggg cac gct gtg   2905
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
        355                 360                 365

ggc atc ttt cgg gct gcc gtg tgc acc cgg ggg gtt gcg aag gcg gtg   2953
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
    370                 375                 380

gac ttt gta ccc gtc gag tct atg gga acc act atg cgg tcc ccg gtc   3001
Asp Phe Val Pro Val Glu Ser Met Gly Thr Thr Met Arg Ser Pro Val
385                 390                 395                 400

ttc acg gac aac tcg tcc cct ccg gcc gta ccg cag aca ttc cag gtg   3049
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln Val
                405                 410                 415

gcc cat cta cac gcc cct act ggt agc ggc aag agc act aag gtg ccg   3097
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
            420                 425                 430

gct gcg tat gca gcc caa ggg tat aag gtg ctt gtc ctg aac ccg tcc   3145
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
        435                 440                 445

gtc gcc gcc acc cta ggt ttc ggg gcg tat atg tct aag gca cat ggt   3193
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
    450                 455                 460
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atc gac cct aac atc aga acc ggg gta agg acc atc acc acg ggt gcc   3241
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
465                 470                 475                 480

ccc atc acg tac tcc acc tat ggc aag ttt ctt gcc gac ggt ggt tgc   3289
Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
                485                 490                 495

tct ggg ggc gcc tat gac atc ata ata tgt gat gag tgc cac tca act   3337
Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
            500                 505                 510

gac tcg acc act atc ctg ggc atc ggc aca gtc ctg gac caa gcg gag   3385
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
        515                 520                 525

acg gct gga gcg cga ctc gtc gtg ctc gcc acc gct acg cct ccg gga   3433
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
    530                 535                 540

tcg gtc acc gtg cca cat cca aac atc gag gag gtg gct ctg tcc agc   3481
Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Ser
545                 550                 555                 560

act gga gaa atc ccc ttt tat ggc aaa gcc atc ccc atc gag acc atc   3529
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Thr Ile
                565                 570                 575

aag ggg ggg agg cac ctc att ttc tgc cat tcc aag aag aaa tgt gat   3577
Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp
            580                 585                 590

gag ctc gcc gcg aag ctg tcc ggc ctc gga ctc aat gct gta gca tat   3625
Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Leu Asn Ala Val Ala Tyr
        595                 600                 605

tac cgg ggc ctt gat gta tcc gtc ata cca act agc gga gac gtc att   3673
Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Ile
    610                 615                 620

gtc gta gca acg gac gct cta atg acg ggc ttt acc ggc gat ttc gac   3721
Val Val Ala Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp
625                 630                 635                 640

tca gtg atc gac tgc aat aca tgt gtc acc cag aca gtc gac ttc agc   3769
Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser
                645                 650                 655

ctg gac ccg acc ttc acc att gag acg acg acc gtg cca caa gac gcg   3817
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
            660                 665                 670

gtg tca cgc tcg cag cgg cga ggc agg act ggt agg ggc agg atg ggc   3865
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met Gly
        675                 680                 685
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att tac agg ttt gtg act cca gga gaa cgg ccc tcg ggc atg ttc gat   3913
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
    690                 695                 700

tcc tcg gtt ctg tgc gag tgc tat gac gcg ggc tgt gct tgg tac gag   3961
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
705                 710                 715                 720

ctc acg ccc gcc gag acc tca gtt agg ttg cgg gct tac cta aac aca   4009
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
                725                 730                 735

cca ggg ttg ccc gtc tgc cag gac cat ctg gag ttc tgg gag agc gtc   4057
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val
            740                 745                 750

ttt aca ggc ctc acc cac ata gac gcc cat ttc ttg tcc cag act aag   4105
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
        755                 760                 765

cag gca gga gac aac ttc ccc tac ctg gta gca tac cag gct acg gtg   4153
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
    770                 775                 780

tgc gcc agg gct cag gct cca cct cca tcg tgg gac caa atg tgg aag   4201
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
785                 790                 795                 800

tgt ctc ata cgg cta aag cct acg ctg cac ggg cca acg ccc ctg ctg   4249
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
                805                 810                 815

tat agg ctg gga gcc gtt caa aac gag gtt act acc aca cac ccc ata   4297
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro Ile
            820                 825                 830

acc aaa tac atc atg gca tgc atg tcg gct gac ctg gag gtc gtc acg   4345
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr
        835                 840                 845

agc acc tgg gtg ctg gta ggc gga gtc cta gca gct ctg gcc gcg tat   4393
Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
    850                 855                 860

tgc ctg aca aca ggc agc gtg gtc att gtg ggc agg atc atc ttg tcc   4441
Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
865                 870                 875                 880

gga aag ccg gcc atc att ccc gac agg gaa gtc ctt tac cgg gag ttc   4489
Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe
                885                 890                 895

gat gag atg gaa gag tgc gcc tca cac ctc cct tac atc gaa cag gga   4537
Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln Gly
            900                 905                 910
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atg cag ctc gcc gaa caa ttc aaa cag aag gca atc ggg ttg ctg caa   4585
Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu Gln
        915                 920                 925

aca gcc acc aag caa gcg gag gct gct gct ccc gtg gtg gaa tcc aag   4633
Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys
    930                 935                 940

tgg cgg acc ctc gaa gcc ttc tgg gcg aag cat atg tgg aat ttc atc   4681
Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe Ile
945                 950                 955                 960

agc ggg ata caa tat tta gca ggc ttg tcc act ctg cct ggc aac ccc   4729
Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro
                965                 970                 975

gcg ata gca tca ctg atg gca ttc aca gcc tct atc acc agc ccg ctc   4777
Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu
            980                 985                 990

acc acc caa cat acc ctc ctg ttt aac atc ctg ggg gga tgg gtg gcc   4825
Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala
        995                 1000                1005

gcc caa ctt gct cct ccc agc gct gct tct gct ttc gta ggc gcc ggc   4873
Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly
    1010                1015                1020

atc gct gga gcg gct gtt ggc agc ata ggc ctt ggg aag gtg ctt gtg   4921
Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val
1025                1030                1035                1040

gat att ttg gca ggt tat gga gca ggg gtg gca ggc gcg ctc gtg gcc   4969
Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala
            1045                1050                1055

ttt aag gtc atg agc ggc gag atg ccc tcc acc gag gac ctg gtt aac   5017
Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn
        1060                1065                1070

cta ctc cct gct atc ctc tcc cct ggc gcc cta gtc gtc ggg gtc gtg   5065
Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val
    1075                1080                1085

tgc gca gcg ata ctg cgt cgg cac gtg ggc cca ggg gag ggg gct gtg   5113
Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val
    1090                1095                1100

cag tgg atg aac cgg ctg ata gcg ttc gct tcg cgg ggt aac cac gtc   5161
Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val
1105                1110                1115                1120

tcc ccc acg cac tat gtg cct gag agc gac gct gca gca cgt gtc act   5209
Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr
            1125                1130                1135
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cag atc ctc tct agt ctt acc atc act cag ctg ctg aag agg ctt cac   5257
Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His
            1140                1145                1150

cag tgg atc aac gag gac tgc tcc acg cca tgc tcc ggc tcg tgg cta   5305
Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu
        1155                1160                1165

aga gat gtt tgg gat tgg gta tgc acg gtg ttg act gat ttc aag acc   5353
Arg Asp Val Trp Asp Trp Val Cys Thr Val Leu Thr Asp Phe Lys Thr
    1170                1175                1180

tgg ctc cag tcc aag ctc ctg ccg cga ttg ccg gga gtc ccc ttc ttc   5401
Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe Phe
1185                1190                1195                1200

tca tgt caa cgt ggg tac aag gga gtc tgg cgg ggc gac ggc atc atg   5449
Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met
                1205                1210                1215

caa acc acc tgc cca tgt gga gca cag atc acc gga cat gtg aaa aac   5497
Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn
            1220                1225                1230

tgt tcc atg agg atc gtg ggg cct agg acc tgt agt aac acg tgg cat   5545
Cys Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp His
        1235                1240                1245

gga aca ttc ccc att aac gcg tac acc acg ggc ccc tgc acg ccc tcc   5593
Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser
    1250                1255                1260

ccg gcg cca aat tat tct agg gcg ctg tgg cgg gtg gct gct gag gag   5641
Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu
1265                1270                1275                1280

tac gtg gag gtt acg cgg gtg ggg gat ttc cac tac gtg acg ggc atg   5689
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met
                1285                1290                1295

acc act gac aac gta aag tgc ccg tgt cag gtt ccg gcc ccc gaa ttc   5737
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe
            1300                1305                1310

ttc aca gaa gtg gat ggg gtg cgg ttg cac agg tac gct cca gcg tgc   5785
Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys
        1315                1320                1325

aaa ccc ctc cta cgg gag gag gtc aca ttc ctg gtc ggg ctc aat caa   5833
Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn Gln
    1330                1335                1340

tac ctg gtt ggg tca cag ctc cca tgc gag ccc gaa ccg gac gta gca   5881
Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala
1345                1350                1355                1360
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gtg ctc act tcc atg ctc acc gac ccc tcc cac att acg gcg gag acg   5929
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr
                1365                1370                1375

gct aag cgt agg ctg gcc agg gga tct ccc ccc tcc ttg gcc agc tca   5977
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser
            1380                1385                1390

tca gct agc cag ctg tct gcg ccc tcc ttg aag gca aca tgc act acc   6025
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr
        1395                1400                1405

cgt cat gac tcc ccg gac gct gac ctc atc gag gcc aac ctc ctg tgg   6073
Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp
    1410                1415                1420

cgg cag gag atg ggc ggg aac atc acc cgc gtg gag tca gaa aat aag   6121
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys
1425                1430                1435                1440

gta gta att ttg gac tct ttc gag ccg ctc caa gcg gag gag gat gag   6169
Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp Glu
                1445                1450                1455

agg gaa gta tcc gtt ccg gcg gag atc ctg cgg agg tcc agg aaa ttc   6217
Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys Phe
            1460                1465                1470

cct cga gcg atg ccc ata tgg gca cgc ccg gat tac aac cct cca ctg   6265
Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu
        1475                1480                1485

tta gag tcc tgg aag gac ccg gac tac gtc cct cca gtg gta cac ggg   6313
Leu Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His Gly
    1490                1495                1500

tgt cca ttg ccg cct gcc aag gcc cct ccg ata cca cct cca cgg agg   6361
Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg Arg
1505                1510                1515                1520

aag agg acg gtt gtc ctg tca gaa tct acc gtg tct tct gcc ttg gcg   6409
Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu Ala
                1525                1530                1535

gag ctc gcc aca aag acc ttc ggc agc tcc gaa tcg tcg gcc gtc gac   6457
Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val Asp
            1540                1545                1550

agc ggc acg gca acg gcc tct cct gac cag ccc tcc gac gac ggc gac   6505
Ser Gly Thr Ala Thr Ala Ser Pro Asp Gln Pro Ser Asp Asp Gly Asp
        1555                1560                1565

gcg gga tcc gac gtt gag tcg tac tcc tcc atg ccc ccc ctt gag ggg   6553
Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly
    1570                1575                1580
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gag ccg ggg gat ccc gat ctc agc gac ggg tct tgg tct acc gta agc   6601
Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser
1585                1590                1595                1600

gag gag gct agt gag gac gtc gtc tgc tgc tcg atg tcc tac aca tgg   6649
Glu Glu Ala Ser Glu Asp Val Val Cys Cys Ser Met Ser Tyr Thr Trp
                1605                1610                1615

aca ggc gcc ctg atc acg cca tgc gct gcg gag gaa acc aag ctg ccc   6697
Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu Pro
            1620                1625                1630

atc aat gca ctg agc aac tct ttg ctc cgt cac cac aac ttg gtc tat   6745
Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr
        1635                1640                1645

gct aca aca tct cgc agc gca agc ctg cgg cag aag aag gtc acc ttt   6793
Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr Phe
    1650                1655                1660

gac aga ctg cag gtc ctg gac gac cac tac cgg gac gtg ctc aag gag   6841
Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys Glu
1665                1670                1675                1680

atg aag gcg aag gcg tcc aca gtt aag gct aaa ctt cta tcc gtg gag   6889
Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val Glu
                1685                1690                1695

gaa gcc tgt aag ctg acg ccc cca cat tcg gcc aga tct aaa ttt ggc   6937
Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe Gly
            1700                1705                1710

tat ggg gca aag gac gtc cgg aac cta tcc agc aag gcc gtt aac cac   6985
Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
        1715                1720                1725

atc cgc tcc gtg tgg aag gac ttg ctg gaa gac act gag aca cca att   7033
Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro Ile
    1730                1735                1740

gac acc acc atc atg gca aaa aat gag gtt ttc tgc gtc caa cca gag   7081
Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu
1745                1750                1755                1760

aag ggg ggc cgc aag cca gct cgc ctt atc gta ttc cca gat ttg ggg   7129
Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly
                1765                1770                1775

gtt cgt gtg tgc gag aaa atg gcc ctt tac gat gtg gtc tcc acc ctc   7177
Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr Leu
            1780                1785                1790

cct cag gcc gtg atg ggc tct tca tac gga ttc caa tac tct cct gga   7225
Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly
        1795                1800                1805
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cag cgg gtc gag ttc ctg gtg aat gct tgg aaa gcg aag aaa tgc cct   7273
Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys Pro
    1810                1815                1820

atg ggc ttc gca tat gac acc cgc tgt ttt gac tca acg gtc act gag   7321
Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
1825                1830                1835                1840

aat gac atc cgt gtt gag gag tca atc tac caa tgt tgt gac ttg gcc   7369
Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu Ala
                1845                1850                1855

ccc gaa gcc aga cag gcc ata agg tcg ctc aca gag cgg ctt tac atc   7417
Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr Ile
            1860                1865                1870

ggg ggc ccc ctg act aat tct aaa ggg cag aac tgc ggc tat cgc cgg   7465
Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg Arg
        1875                1880                1885

tgc cgc gcg agc ggt gta ctg acg acc agc tgc ggt aat acc ctc aca   7513
Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr
    1890                1895                1900

tgt tac ttg aag gcc gct gcg gcc tgt cga gct gcg aag ctc cag gac   7561
Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln Asp
1905                1910                1915                1920

tgc acg atg ctc gta tgc gga gac gac ctt gtc gtt atc tgt gaa agc   7609
Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser
                1925                1930                1935

gcg ggg acc caa gag gac gag gcg agc cta cgg gcc ttc acg gag gct   7657
Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu Ala
            1940                1945                1950

atg act aga tac tct gcc ccc cct ggg gac ccg ccc aaa cca gaa tac   7705
Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu Tyr
        1955                1960                1965

gac ttg gag ttg ata aca tca tgc tcc tcc aat gtg tca gtc gcg cac   7753
Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His
    1970                1975                1980

gat gca tct ggc aaa agg gtg tac tat ctc acc cgt gac ccc acc acc   7801
Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
1985                1990                1995                2000

ccc ctt gcg cgg gct gcg tgg gag aca gct aga cac act cca gtc aat   7849
Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn
                2005                2010                2015

tcc tgg cta ggc aac atc atc atg tat gcg ccc acc ttg tgg gca agg   7897
Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg
            2020                2025                2030
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atg atc ctg atg act cat ttc ttc tcc atc ctt cta gct cag gaa caa   7945
Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln
        2035                2040                2045

ctt gaa aaa gcc cta gat tgt cag atc tac ggg gcc tgt tac tcc att   7993
Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile
    2050                2055                2060

gag cca ctt gac cta cct cag atc att caa cga ctc cac ggc ctt agc   8041
Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu Ser
2065                2070                2075                2080

gca ttt tca ctc cat agt tac tct cca ggt gag atc aat agg gtg gct   8089
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
                2085                2090                2095

tca tgc ctc agg aaa ctt ggg gta ccg ccc ttg cga gtc tgg aga cat   8137
Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg His
            2100                2105                2110

cgg gcc aga agt gtc cgc gct agg cta ctg tcc cag ggg ggg agg gct   8185
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg Ala
        2115                2120                2125

gcc act tgt ggc aag tac ctc ttc aac tgg gca gta agg acc aag ctc   8233
Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
    2130                2135                2140

aaa ctc act cca atc ccg gct gcg tcc cag ttg gat tta tcc agc tgg   8281
Lys Leu Thr Pro Ile Pro Ala Ala Ser Gln Leu Asp Leu Ser Ser Trp
2145                2150                2155                2160

ttc gtt gct ggt tac agc ggg gga gac ata tat cac agc ctg tct cgt   8329
Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser Arg
                2165                2170                2175

gcc cga ccc cgc tgg ttc acg tgg tgc cta ctc cta ctt tct gta ggg   8377
Ala Arg Pro Arg Trp Phe Thr Trp Cys Leu Leu Leu Leu Ser Val Gly
            2180                2185                2190

gta ggc atc tat cta ctc ccc aac cga tga acggggagct aaacactcca     8427
Val Gly Ile Tyr Leu Leu Pro Asn Arg  *
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c atg gac cgg gag atg gca gca tcg tgc gga ggc gcg gtt ttc gta ggt 1849
  Met Asp Arg Glu Met Ala Ala Ser Cys Gly Gly Ala Val Phe Val Gly
   1               5                  10                  15

ctg ata ctc ttg acc ttg tca ccg cac tat aag ctg ttc ctc gct agg   1897
Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala Arg
            20                  25                  30

ctc ata tgg tgg tta caa tat ttt atc acc agg gcc gag gca cac ttg   1945
Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His Leu
        35                  40                  45

caa gtg tgg atc ccc ccc ctc aac gtt cgg ggg ggc cgc gat gcc gtc   1993
Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
     50                  55                  60

atc ctc ctc acg tgc gcg atc cac cca gag cta atc ttt acc atc acc   2041
Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile Thr
 65                  70                  75                  80

aaa atc ttg ctc gcc ata ctc ggt cca ctc atg gtg ctc cag gct ggt   2089
Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly
                85                  90                  95

ata acc aaa gtg ccg tac ttc gtg cgc gca cac ggg ctc att cgt gca   2137
Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg Ala
            100                 105                 110
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tgc atg ctg gtg cgg aag gtt gct ggg ggt cat tat gtc caa atg gct   2185
Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala
        115                 120                 125

ctc atg aag ttg gcc gca ctg aca ggt acg tac gtt tat gac cat ctc   2233
Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His Leu
    130                 135                 140

acc cca ctg cgg gac tgg gcc cac gcg ggc cta cga gac ctt gcg gtg   2281
Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala Val
145                 150                 155                 160

gca gtt gag ccc gtc gtc ttc tct gat atg gag acc aag gtt atc acc   2329
Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile Thr
                165                 170                 175

tgg ggg gca gac acc gcg gcg tgt ggg gac atc atc ttg ggc ctg ccc   2377
Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
            180                 185                 190

gtc tcc gcc cgc agg ggg agg gag ata cat ctg gga ccg gca gac agc   2425
Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp Ser
        195                 200                 205

ctt gaa ggg cag ggg tgg cga ctc ctc gcg cct att acg gcc tac tcc   2473
Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser
    210                 215                 220

caa cag acg cga ggc cta ctt ggc tgc atc atc act agc ctc aca ggc   2521
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
225                 230                 235                 240

cgg gac agg aac cag gtc gag ggg gag gtc caa gtg gtc tcc acc gca   2569
Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
                245                 250                 255

aca caa tct ttc ctg gcg acc tgc gtc aat ggc gtg tgt tgg act gtc   2617
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
            260                 265                 270

tat cat ggt gcc ggc tca aag acc ctt gcc ggc cca aag ggc cca atc   2665
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
        275                 280                 285

acc caa atg tac acc aat gtg gac cag gac ctc gtc ggc tgg caa gcg   2713
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
    290                 295                 300

ccc ccc ggg gcg cgt tcc ttg aca cca tgc acc tgc ggc agc tcg gac   2761
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
305                 310                 315                 320

ctt tac ttg gtc acg agg cat gcc gat gtc att ccg gtg cgc cgg cgg   2809
Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg
                325                 330                 335
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ggc gac ggc agg ggg agc cta ctc tcc ccc agg ccc gtc tcc tac ttg   2857
Gly Asp Gly Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
            340                 345                 350

aag ggc tct tcg ggc ggt cca ctg ctc tgc ccc tcg ggg cac gct gtg   2905
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
        355                 360                 365

ggc atc ttt cgg gct gcc gtg tgc acc cga ggg gtt gcg aag gcg gtg   2953
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
    370                 375                 380

gac ttt gta ccc gtc gag tct atg gga acc act atg cgg tcc ccg gtc   3001
Asp Phe Val Pro Val Glu Ser Met Gly Thr Thr Met Arg Ser Pro Val
385                 390                 395                 400

ttc acg gac aac tcg tcc cct ccg gcc gta ccg cag aca ttc cag gtg   3049
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln Val
                405                 410                 415

gcc cat cta cac gcc cct act ggt agc ggc aag agc act aag gtg ccg   3097
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
            420                 425                 430

gct gcg tat gca gcc caa ggg tat aag gtg ctt gtc ctg aac ccg tcc   3145
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
        435                 440                 445

gtc gcc gcc acc cta ggt ttc ggg gcg tat atg tct aag gca cat ggt   3193
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
    450                 455                 460

atc gac cct aac atc aga acc ggg gta agg acc atc acc acg ggt gcc   3241
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
465                 470                 475                 480

ccc atc acg tac tcc acc tat ggc aag ttt ctt gcc gac ggt ggt tgc   3289
Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
                485                 490                 495

tct ggg ggc gcc tat gac atc ata ata tgt gat gag tgc cac tca act   3337
Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
            500                 505                 510

gac tcg acc act atc ctg ggc atc ggc aca gtc ctg gac caa gcg gag   3385
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
        515                 520                 525

acg gct gga gcg cga ctc gtc gtg ctc gcc acc gct acg cct ccg gga   3433
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
    530                 535                 540

tcg gtc acc gtg cca cat cca aac atc gag gag gtg gct ctg tcc agc   3481
Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Ser
545                 550                 555                 560
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act gga gaa atc ccc ttt tat ggc aaa gcc atc ccc atc gag acc atc 3529
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Thr Ile
565 570 575

aag ggg ggg agg cac ctc att ttc tgc cat tcc aag aag aaa tgt gat 3577
Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp
580 585 590

gag ctc gcc gcg aag ctg tcc ggc ctc gga ctc aat gct gta gca tat 3625
Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Leu Asn Ala Val Ala Tyr
595 600 605

tac cgg ggc ctt gat gta tcc gtc ata cca act agc gga gac gtc att 3673
Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Ile
610 615 620

gtc gta gca acg gac gct cta atg acg ggc ttt acc ggc gat ttc gac 3721
Val Val Ala Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp
625 630 635 640

tca gtg atc gac tgc aat aca tgt gtc acc cag aca gtc gac ttc agc 3769
Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser
645 650 655

ctg gac ccg acc ttc acc att gag acg acg acc gtg cca caa gac gcg 3817
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
660 665 670

gtg tca cgc tcg cag cgg cga ggc agg act ggt agg ggc agg atg ggc 3865
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met Gly
675 680 685

att tac agg ttt gtg act cca gga gaa cgg ccc tcg ggc atg ttc gat 3913
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
690 695 700

tcc tcg gtt ctg tgc gag tgc tat gac gcg ggc tgt gct tgg tac gag 3961
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
705 710 715 720

ctc acg ccc gcc gag acc tca gtt agg ttg cgg gct tac cta aac aca 4009
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
725 730 735

cca ggg ttg ccc gtc tgc cag gac cat ctg gag ttc tgg gag agc gtc 4057
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val
740 745 750

ttt aca ggc ctc acc cac ata gac gcc cat ttc ttg tcc cag act aag 4105
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
755 760 765

cag gca gga gac aac ttc ccc tac ctg gta gca tac cag gct acg gtg 4153
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
770 775 780

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tgc gcc agg gct cag gct cca cct cca tcg tgg gac caa atg tgg aag   4201
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
785                 790                 795                 800

tgt ctc ata cgg cta aag cct acg ctg cac ggg cca acg ccc ctg ctg   4249
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
                805                 810                 815

tat agg ctg gga gcc gtt caa aac gag gtt act acc aca cac ccc ata   4297
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro Ile
            820                 825                 830

acc aaa tac atc atg gca tgc atg tcg gct gac ctg gag gtc gtc acg   4345
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr
        835                 840                 845

agc acc tgg gtg ctg gta ggc gga gtc cta gca gct ctg gcc gcg tat   4393
Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
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tgc ctg aca aca ggc agc gtg gtc att gtg ggc agg atc atc ttg tcc   4441
Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
865                 870                 875                 880

gga aag ccg gcc atc att ccc gac agg gaa gtc ttt tac cgg gag ttc   4489
Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Phe Tyr Arg Glu Phe
                885                 890                 895

gat gag atg gaa gag tgc gcc tca cac ctc cct tac atc gaa cag gga   4537
Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln Gly
            900                 905                 910

atg cag ctc gcc gaa caa ttc aaa cag aag gca atc ggg ttg ctg caa   4585
Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu Gln
        915                 920                 925

aca gcc acc aag caa gcg gag gct gct gct ccc gtg gtg gaa tcc aag   4633
Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys
    930                 935                 940

tgg cgg acc ctc gaa gcc ttc tgg gcg aag cat atg tgg aat ttc atc   4681
Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe Ile
945                 950                 955                 960

agc ggg ata caa tat tta gca ggc ttg tcc act ctg cct ggc aac ccc   4729
Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro
                965                 970                 975

gcg ata gca tca ctg atg gca ttc aca gcc tct atc acc agc ccg ctc   4777
Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu
            980                 985                 990

acc acc caa cat acc ctc ctg ttt aac atc ctg ggg gga tgg gtg gcc   4825
Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala
        995                 1000                1005
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gcc caa ctt gct cct ccc agc gct gct tct gct ttc gta ggc gcc ggc   4873
Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly
    1010                1015                1020

atc gct gga gcg gct gtt ggc agc ata ggc ctt ggg aag gtg ctt gtg   4921
Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val
1025                1030                1035                1040

gat att ttg gca ggt tat gga gca ggg gtg gca ggc gcg ctc gtg gcc   4969
Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala
                1045                1050                1055

ttt aag gtc atg agc ggc gag atg ccc tcc acc gag gac ctg gtt aac   5017
Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn
            1060                1065                1070

cta ctc cct gct atc ctc tcc cct ggc gcc cta gtc gtc ggg gtc gtg   5065
Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val
        1075                1080                1085

tgc gca gcg ata ctg cgt cgg cac gtg ggc cca ggg gag ggg gct gtg   5113
Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val
    1090                1095                1100

cag tgg atg aac cgg ctg ata gcg ttc gct tcg cgg ggt aac cac gtc   5161
Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val
1105                1110                1115                1120

tcc ccc acg cac tat gtg cct gag agc gac gct gca gca cgt gtc act   5209
Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr
                1125                1130                1135

cag atc ctc tct agt ctt acc atc act cag ctg ctg aag agg ctt cac   5257
Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His
            1140                1145                1150

cag tgg atc aac gag gac tgc tcc acg cca tgc tcc ggc tcg tgg cta   5305
Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu
        1155                1160                1165

aga gat gtt tgg gat tgg ata tgc acg gtg ttg act gat ttc aag acc   5353
Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys Thr
    1170                1175                1180

tgg ctc cag tcc aag ctc ctg ccg cga ttg ccg gga gtc ccc ttc ttc   5401
Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe Phe
1185                1190                1195                1200

tca tgt caa cgt ggg tac aag gga gtc tgg cgg ggc gac ggc atc atg   5449
Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met
                1205                1210                1215

caa acc acc tgc cca tgt gga gca cag atc acc gga cat gtg aaa aac   5497
Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn
            1220                1225                1230
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cgt tcc atg agg atc gtg ggg cct agg acc tgt agt aac acg tgg cat   5545
Arg Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp His
        1235                1240                1245

gga aca ttc ccc att aac gcg tac acc acg ggc ccc tgc acg ccc tcc   5593
Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser
    1250                1255                1260

ccg gcg cca aat tat tct agg gcg ctg tgg cgg gtg gct gct gag gag   5641
Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu
1265                1270                1275                1280

tac gtg gag gtt acg cgg gtg ggg gat ttc cac tac gtg acg ggc atg   5689
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met
                1285                1290                1295

acc act gac aac gta aag tgc ccg tgt cag gtt ccg gcc ccc gaa ttc   5737
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe
            1300                1305                1310

ttc aca gaa gtg gat ggg gtg cgg ttg cac agg tac gct cca gcg tgc   5785
Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys
        1315                1320                1325

aaa ccc ctc cta cgg gag gag gtc aca ttc ctg gtc ggg ctc aat caa   5833
Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn Gln
    1330                1335                1340

tac ctg gtt ggg tca cag ctc cca tgc gag ccc gaa ccg gac gta gca   5881
Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala
1345                1350                1355                1360

gtg ctc act tcc atg ctc acc gac ccc tcc cac att acg gcg gag acg   5929
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr
                1365                1370                1375

gct aag cgt agg ctg gcc agg gga tct ccc ccc tcc ttg gcc agc tca   5977
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser
            1380                1385                1390

tca gct agc cag ctg tct gcg cct tcc ttg aag gca aca tgc act acc   6025
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr
        1395                1400                1405

cgt cat gac tcc ccg gac gct gac ctc atc gag gcc aac ctc ctg tgg   6073
Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp
    1410                1415                1420

cgg cag gag atg ggc ggg aac atc acc cgc gtg gag tca gaa aat aag   6121
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys
1425                1430                1435                1440

gta gta att ttg gac tct ttc gag ccg ctc caa gcg gag gag gat gag   6169
Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp Glu
                1445                1450                1455
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agg gaa gta tcc gtt ccg gcg gag atc ctg cgg agg tcc agg aaa ttc   6217
Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys Phe
            1460                1465                1470

cct cga gcg atg ccc ata tgg gca cgc ccg gat tac aac cct cca ctg   6265
Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu
        1475                1480                1485

tta gag tcc tgg aag gac ccg gac tac gtc cct cca gtg gta cac ggg   6313
Leu Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His Gly
    1490                1495                1500

tgt cca ctg ccg cct gcc aag gcc cct ccg ata cca cct cca cgg agg   6361
Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg Arg
1505                1510                1515                1520

aag agg acg gtt gtc ctg tca gaa tct acc gtg tct tct gcc ttg gcg   6409
Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu Ala
                1525                1530                1535

gag ctc gcc aca aag acc ttc ggc agc tcc gaa tcg tcg gcc gtc gac   6457
Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val Asp
            1540                1545                1550

agc ggc acg gca acg gcc tct cct gac cag ccc tcc gac gac ggc gac   6505
Ser Gly Thr Ala Thr Ala Ser Pro Asp Gln Pro Ser Asp Asp Gly Asp
        1555                1560                1565

gcg gga tcc gac gtt gag tcg tac tcc tcc atg ccc ccc ctt gag ggg   6553
Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly
    1570                1575                1580

gag ccg ggg gat ccc gat ctc agc gac ggg cct tgg tct acc gta agc   6601
Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Pro Trp Ser Thr Val Ser
1585                1590                1595                1600

gag gag gct agt gag gac gtc gtc tgc tgc tcg atg tcc tac aca tgg   6649
Glu Glu Ala Ser Glu Asp Val Val Cys Cys Ser Met Ser Tyr Thr Trp
                1605                1610                1615

aca ggc gcc ctg atc acg cca tgc gct gcg gag gaa acc aag ctg ccc   6697
Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu Pro
            1620                1625                1630

atc aat gca ctg agc aac tct ttg ctc cgt cac cac aac ttg gtc tat   6745
Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr
        1635                1640                1645

gct aca aca tct cgc agc gca agc ctg cgg cag aag aag gtc acc ttt   6793
Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr Phe
    1650                1655                1660

gac aga ctg cag gtc ctg gac gac cac tac cgg gac gtg ctc aag gag   6841
Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys Glu
1665                1670                1675                1680
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atg aag gcg aag gcg tcc aca gtt aag gct aaa ctt cta tcc gtg gag   6889
Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val Glu
                1685                1690                1695

gaa gcc tgt aag ctg acg ccc cca cat tcg gcc aga tct aaa ttt ggc   6937
Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe Gly
            1700                1705                1710

tat ggg gca aag gac gtc cgg aac cta tcc agc aag gcc gtt aac cac   6985
Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
        1715                1720                1725

atc cgc tcc gtg tgg aag gac ttg ctg gaa gac act gag aca cca att   7033
Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro Ile
    1730                1735                1740

gac acc acc atc atg gca aaa aat gag gtt ttc tgc gtc caa cca gag   7081
Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu
1745                1750                1755                1760

aag ggg ggc cgc aag cca gct cgc ctt atc gta ttc cca gat ttg ggg   7129
Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly
                1765                1770                1775

gtt cgt gtg tgc gag aaa atg gcc ctt tac gat gtg gtc tcc acc ctc   7177
Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr Leu
            1780                1785                1790

cct cag gcc gtg atg ggc tct tca tac gga ttc caa tac tct cct gga   7225
Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly
        1795                1800                1805

cag cgg gtc gag ttc ctg gtg aat gcc tgg aaa gcg aag aaa tgc cct   7273
Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys Pro
    1810                1815                1820

atg ggc ttc gca tat gac acc cgc tgt ttt gac tca acg gtc act gag   7321
Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
1825                1830                1835                1840

aat gac atc cgt gtt gag gag tca atc tac caa tgt tgt gac ttg gcc   7369
Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu Ala
                1845                1850                1855

ccc gaa gcc aga cag gcc ata agg tcg ctc aca gag cgg ctt tac atc   7417
Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr Ile
            1860                1865                1870

ggg ggc ccc ctg act aat tct aaa ggg cag aac tgc ggc tat cgc cgg   7465
Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg Arg
        1875                1880                1885

tgc cgc gcg agc ggt gta ctg acg acc agc tgc ggt aat acc ctc aca   7513
Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr
    1890                1895                1900
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tgt tac ttg aag gcc gct gcg gcc tgt cga gct gcg aag ctc cag gac   7561
Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln Asp
1905                 1910                 1915                 1920

tgc acg atg ctc gta tgc gga gac gac ctt gtc gtt atc tgt gaa agc   7609
Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser
                1925                 1930                 1935

gcg ggg acc caa gag gac gag gcg agc cta cgg gcc ttc acg gag gct   7657
Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu Ala
            1940                 1945                 1950

atg act aga tac tct gcc ccc cct ggg gac ccg ccc aaa cca gaa tac   7705
Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu Tyr
        1955                 1960                 1965

gac ttg gag ttg ata aca tca tgc tcc tcc aat gtg tca gtc gcg cac   7753
Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His
    1970                 1975                 1980

gat gca tct ggc aaa agg gtg tac tat ctc acc cgt gac ccc acc acc   7801
Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
1985                 1990                 1995                 2000

ccc ctt gcg cgg gct gcg tgg gag aca gct aga cac act cca gtc aat   7849
Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn
                2005                 2010                 2015

tcc tgg cta ggc aac atc atc atg tat gcg ccc acc ttg tgg gca agg   7897
Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg
            2020                 2025                 2030

atg atc ctg atg act cat ttc ttc tcc atc ctt cta gct cag gaa caa   7945
Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln
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ctt gaa aaa gcc cta gat tgt cag atc tac ggg gcc tgt tac tcc att   7993
Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile
    2050                 2055                 2060

gag cca ctt gac cta cct cag atc att caa cga ctc cac ggc ctt agc   8041
Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu Ser
2065                 2070                 2075                 2080

gca ttt tca ctc cat agt tac tct cca ggt gag atc aat agg gtg gct   8089
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
                2085                 2090                 2095

tca tgc ctc agg aaa ctt ggg gta ccg ccc ttg cga gtc tgg aga cat   8137
Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg His
            2100                 2105                 2110

cgg gcc aga agt gtc cgc gct agg cta ctg tcc cag ggg ggg agg gct   8185
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg Ala
        2115                 2120                 2125
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gcc act tgt ggc aag tac ctc ttc aac tgg gca gta agg acc aag ctc   8233
Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
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aaa ctc act cca atc ccg gct gcg tcc cag ttg gat tta tcc agc tgg   8281
Lys Leu Thr Pro Ile Pro Ala Ala Ser Gln Leu Asp Leu Ser Ser Trp
2145                2150                2155                2160

ttc gtt gct ggt tac agc ggg gga gac ata tat cac agc ctg tct cgt   8329
Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser Arg
                2165                2170                2175

gcc cga ccc cgc tgg ttc atg tgg tgc cta ctc cta ctt tct gta ggg   8377
Ala Arg Pro Arg Trp Phe Met Trp Cys Leu Leu Leu Leu Ser Val Gly
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gta ggc atc tat cta ctc ccc aac cga tga acggggagct aaacactcca     8427
Val Gly Ile Tyr Leu Leu Pro Asn Arg  *
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c atg gac cgg gag atg gca gca tcg tgc gga ggc gcg gtt ttc gta ggt 1849
  Met Asp Arg Glu Met Ala Ala Ser Cys Gly Gly Ala Val Phe Val Gly
   1               5                  10                  15

ctg ata ctc ttg acc ttg tca ccg cac tat aag ctg ttc ctc gct agg   1897
Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala Arg
            20                  25                  30

ctc ata tgg tgg tta caa tat ttt atc acc agg gcc gag gca cac ttg   1945
Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His Leu
        35                  40                  45

caa gtg tgg atc ccc ccc ctc aac gtt cgg ggg ggc cgc gat gcc gtc   1993
Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
    50                  55                  60

atc ctc ctc acg tgc gcg atc cac cca gag cta atc ttt acc atc acc   2041
Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile Thr
65                  70                  75                  80

aaa atc ttg ctc gcc ata ctc ggt cca ctc atg gtg ctc cag gct ggt   2089
Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly
                85                  90                  95

ata acc aaa gtg ccg tac ttc gtg cgc gca cac ggg ctc att cgt gca   2137
Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg Ala
            100                 105                 110

tgc atg ctg gtg cgg aag gtt gct ggg ggt cat tat gtc caa atg gct   2185
Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala
        115                 120                 125

ctc atg aag ttg gcc gca ctg aca ggt acg tac gtt tat gac cat ctc   2233
Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His Leu
    130                 135                 140

acc cca ctg cgg gac tgg gcc cac gcg ggc cta cga gac ctt gcg gtg   2281
Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala Val
145                 150                 155                 160

gca gtt gag ccc gtc gtc ttc tct gat atg gag acc aag gtt atc acc   2329
Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile Thr
                165                 170                 175

tgg ggg gca gac acc gcg gcg tgt ggg gac atc atc ttg ggc ctg ccc   2377
Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
            180                 185                 190

gtc tcc gcc cgc agg ggg agg gag ata cat ctg gga ccg gca gac agc   2425
Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp Ser
        195                 200                 205
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ctt gaa ggg cag ggg tgg cga ctc ctc gcg cct att acg gcc tac tcc   2473
Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser
    210                 215                 220

caa cag acg cga ggc cta ctt ggc tgc atc atc acc agc ctc aca ggc   2521
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
225                 230                 235                 240

cgg gac agg aac cag gtc gag ggg gag gtc caa gtg gtc tcc acc gca   2569
Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
                245                 250                 255

aca caa tct ttc ctg gcg acc tgc gtc aat ggc gtg tgt tgg act gtc   2617
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
            260                 265                 270

tat cat ggt gcc ggc tca aag acc ctt gcc ggc cca aag ggc cca atc   2665
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
        275                 280                 285

acc caa atg tac acc aat gtg gac cag gac ctc gtc ggc tgg caa gcg   2713
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
    290                 295                 300

ccc ccc ggg gcg cgt tcc ttg aca cca tgc acc tgc ggc agc tcg gac   2761
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
305                 310                 315                 320

ctt tac ttg gtc acg aag cat gcc gat gtc att ccg gtg cgc cgg cgg   2809
Leu Tyr Leu Val Thr Lys His Ala Asp Val Ile Pro Val Arg Arg Arg
                325                 330                 335

ggc gac agc agg ggg agc cta ctc tcc ccc cgg ccc gtc tcc tac ttg   2857
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
            340                 345                 350

aag ggc tct tcg ggc ggt cca ctg ctc tgc ccc tcg ggg cac gct gtg   2905
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
        355                 360                 365

ggc atc ttt cgg gct gcc gtg tgc acc cga ggg gtt gcg aag gcg gtg   2953
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
    370                 375                 380

gac ttt gta ccc gtc gag tct atg gaa acc act atg cgg tcc ccg gtc   3001
Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val
385                 390                 395                 400

ttc acg gac aac tcg tcc cct ccg gcc gta ccg cag aca ttc cag gtg   3049
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln Val
                405                 410                 415

gcc cat cta cac gcc cct act ggt agc ggc aag agc act aag gtg ccg   3097
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
            420                 425                 430
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gct gcg tat gca gcc caa ggg tat aag gtg ctt gtc ctg aac ccg tcc   3145
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
        435                 440                 445

gtc gcc gcc acc cta ggt ttc ggg gcg tat atg tct aag gca cat ggt   3193
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
    450                 455                 460

atc gac cct aac atc aga acc ggg gta agg acc atc acc acg ggt gcc   3241
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
465                 470                 475                 480

ccc atc acg tac tcc acc tat ggc aag ttt ctt gcc gac ggt ggt tgc   3289
Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
                485                 490                 495

tct ggg ggc gcc tat gac atc ata ata tgt gat gag tgc cac tca act   3337
Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
            500                 505                 510

gac tcg acc act atc ctg ggc atc ggc aca gtc ctg gac caa gcg gag   3385
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
        515                 520                 525

acg gct gga gcg cga ctc gtc gtg ctc gcc acc gct acg cct ccg gga   3433
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
    530                 535                 540

tcg gtc acc gtg cca cat cca aac atc gag gag gtg gct ctg tcc agc   3481
Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Ser
545                 550                 555                 560

act gga gaa atc ccc ttt tat ggc aaa gcc atc ccc atc gag acc atc   3529
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Thr Ile
                565                 570                 575

aag ggg ggg agg cac ctc att ttc tgc cat tcc aag aag aaa tgc gat   3577
Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp
            580                 585                 590

gag ctc gcc gcg aag ctg tcc ggc ctc gga ctc aat gct gta gca tat   3625
Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Leu Asn Ala Val Ala Tyr
        595                 600                 605

tac cgg ggc ctt gat gta tcc gtc ata cca act agc gga gac gtc att   3673
Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Ile
    610                 615                 620

gtc gta gca acg gac gct cta atg acg ggc ttt acc ggc gat ttc gac   3721
Val Val Ala Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp
625                 630                 635                 640

tca gtg atc gac tgc aat aca tgt gtc acc cag aca gtc gac ttc agc   3769
Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser
                645                 650                 655
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ctg gac ccg acc ttc acc att gag acg acg acc gtg cca caa gac gcg   3817
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
            660                 665                 670

gtg tca cgc tcg cag cgg cga ggc agg act ggt agg ggc agg atg ggc   3865
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met Gly
        675                 680                 685

att tac agg ttt gtg act cca gga gaa cgg ccc tcg ggc atg ttc gat   3913
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
    690                 695                 700

tcc tcg gtt ctg tgc gag tgc tat gac gcg ggc tgt gct tgg tac gag   3961
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
705                 710                 715                 720

ctc acg ccc gcc gag acc tca gtt agg ttg cgg gct tac cta aac aca   4009
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
                725                 730                 735

cca ggg ttg ccc gtc tgc cag gac cat ctg gag ttc tgg gag ggc gtc   4057
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly Val
            740                 745                 750

ttt aca ggc ctc acc cac ata gac gcc cat ttc ttg tcc cag act aag   4105
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
        755                 760                 765

cag gca gga gac aac ttc ccc tac ctg gta gca tac cag gct acg gtg   4153
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
    770                 775                 780

tgc gcc agg gct cag gct cca cct cca tcg tgg gac caa atg tgg aag   4201
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
785                 790                 795                 800

tgt ctc ata cgg cta aag cct acg ctg cac ggg cca acg ccc ctg ctg   4249
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
                805                 810                 815

tat agg ctg gga gcc gtt caa aac gag gtt act acc aca cac ccc ata   4297
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro Ile
            820                 825                 830

acc aaa tac atc atg gca tgc atg tcg gct gac ctg gag gtc gtc acg   4345
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr
        835                 840                 845

agc acc tgg gtg ctg gta ggc gga gtc cta gca gct ctg gct gcg tat   4393
Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
    850                 855                 860

tgc ctg aca aca ggc agc gtg gtc att gtg ggc agg atc atc ttg tcc   4441
Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
865                 870                 875                 880
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gga agg ccg gcc atc att ccc gac agg gaa gtc ctt tac cgg gag ttc   4489
Gly Arg Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe
                885                 890                 895

gat gag atg gaa gag tgt gcc tca cac ctc cct tac atc gaa cag gga   4537
Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln Gly
            900                 905                 910

atg cag ctc gcc gaa caa ttc aaa cag aag gca atc ggg ttg ctg caa   4585
Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu Gln
        915                 920                 925

aca gcc acc aag caa gcg gag gct gct gct ccc gtg gtg gaa tcc aag   4633
Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys
    930                 935                 940

tgg cgg acc ctc gaa gcc ttc tgg gcg aag cat atg tgg aat ttc atc   4681
Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe Ile
945                 950                 955                 960

agc ggg ata caa tat tta gca ggc ttg tcc act ctg cct ggc aac ccc   4729
Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro
                965                 970                 975

gcg ata gca tca ctg atg gca ttc aca gcc tct atc acc agc ccg ctc   4777
Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu
            980                 985                 990

acc acc caa cat acc ctc ctg ttt aac atc ctg ggg gga tgg gtg gcc   4825
Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala
        995                 1000                1005

gcc caa ctt gct cct ccc agc gct gct tcc gct ttc gta ggc gcc ggc   4873
Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly
    1010                1015                1020

atc gct gga gcg gct gtt ggc agc ata ggc ctt ggg aag gtg ctt gtg   4921
Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val
1025                1030                1035                1040

gat att ttg gca ggt tat gga gca ggg gtg gca ggc gcg ctc gtg gcc   4969
Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala
                1045                1050                1055

ttt aag gtc atg agc ggc gag atg ccc tcc acc gag gac ctg gtt aac   5017
Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn
            1060                1065                1070

cta ctc cct gct atc ctc tcc cct ggc gcc cta gtc gtc ggg gtc gtg   5065
Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val
        1075                1080                1085

tgc gca gcg ata ctg cgt cgg cac gtg ggc cca ggg gag ggg gct gtg   5113
Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val
    1090                1095                1100
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cag tgg atg aac cgg ctg ata gcg ttc gct tcg cgg ggt aac cac gtc   5161
Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val
1105                1110                1115                1120

tcc ccc acg cac tat gtg cct gag agc gac gct gca gca cgt gtc act   5209
Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr
                    1125                1130                1135

cag atc ctc tct agt ctt acc atc act cag ctg ctg aag agg ctt cac   5257
Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His
            1140                1145                1150

cag tgg atc aac gag gac tgc tcc acg cca tgc tcc ggc tcg tgg cta   5305
Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu
        1155                1160                1165

aga gat gtt tgg gat tgg ata tgc acg gtg ttg act gat ttc aag gcc   5353
Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys Ala
    1170                1175                1180

tgg ctc cag tcc aag ctc ctg ccg cga ttg ccg gga gtc ccc ttc ttc   5401
Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe Phe
1185                1190                1195                1200

tca tgt caa cgt ggg tac aag gga gtc tgg cgg ggc gac ggc atc atg   5449
Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met
                    1205                1210                1215

caa acc acc tgc cca tgt gga gca cag atc acc gga cat gtg aaa aac   5497
Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn
            1220                1225                1230

tgt tcc atg agg atc gtg ggg cct agg acc tgt agt aac acg tgg cat   5545
Cys Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp His
        1235                1240                1245

gga aca ttc ccc att aac gcg tac acc acg ggc ccc tgc acg ccc tcc   5593
Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser
    1250                1255                1260

ccg gcg cca aat tat tct agg gcg ctg tgg cgg gtg gct gct gag gag   5641
Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu
1265                1270                1275                1280

tac gtg gag gtt acg cga gtg ggg gat ttc cac tac gtg acg ggc atg   5689
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met
                    1285                1290                1295

acc act gac aac gta aag tgc ccg tgt cag gtt ccg gcc ccc gaa ttc   5737
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe
            1300                1305                1310

ttc aca gaa gtg gat ggg gtg cgg ttg cac agg tac gct cca gcg tgc   5785
Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys
        1315                1320                1325
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aaa ccc ctc cta cgg gag gag gtc aca ttc ctg gtc ggg ctc aat caa   5833
Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn Gln
    1330                1335                1340

tac ccg gtt ggg tca cag ctc cca tgc gag ccc gaa ctg gac gta gca   5881
Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Leu Asp Val Ala
1345                1350                1355                1360

gtg ctc act tcc atg ctc acc gac ccc tcc cac att acg gcg gag acg   5929
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr
                1365                1370                1375

gct aag cgt agg ctg gcc agg gga tct ccc ccc tcc ttg gcc agc tca   5977
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser
            1380                1385                1390

tca gct agc cag ctg tct gcg cct tcc ttg aag gca aca tgc act acc   6025
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr
        1395                1400                1405

cgt cat gac tcc ccg gac gct gac ctc atc gag gcc aac ctc ctg tgg   6073
Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp
    1410                1415                1420

cgg cag gag atg ggc ggg aac atc acc cgc gtg gag tca gag aat aag   6121
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys
1425                1430                1435                1440

gta gta att ttg gac tct ttc gag ccg ctc caa gcg gag gag gat gag   6169
Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp Glu
                1445                1450                1455

agg gaa gta tcc gtt ccg gcg gag atc ctg cgg agg tcc agg aaa ttc   6217
Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys Phe
            1460                1465                1470

cct cga gcg atg ccc ata tgg gca cgc ccg gat tac aac cct cca ctg   6265
Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu
        1475                1480                1485

tta gag tcc tgg aag gac ccg gac tac gtc cct cca gtg gta cac ggg   6313
Leu Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His Gly
    1490                1495                1500

tgt cca ttg ccg cct gcc aag gcc cct ccg ata cca cct cca cgg agg   6361
Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg Arg
1505                1510                1515                1520

aag agg acg gtt gtc ctg tca gaa tct acc gtg tct tct gcc ttg gcg   6409
Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu Ala
                1525                1530                1535

gag ctc gcc aca aag acc ttc ggc agc tcc gaa tcg tcg gcc gtc gac   6457
Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val Asp
            1540                1545                1550
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agc ggc acg gca acg gcc tct cct gac cag ccc tcc gac gac ggc gac   6505
Ser Gly Thr Ala Thr Ala Ser Pro Asp Gln Pro Ser Asp Asp Gly Asp
        1555                1560                1565

gcg gga tcc gac gtt gag tcg tac tcc tcc atg ccc ccc ctt gag ggg   6553
Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly
    1570                1575                1580

gag ccg ggg gat ccc gat ctc agc gac ggg tct tgg tct acc gta agc   6601
Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser
1585                1590                1595                1600

gag gag gct agt gag gac gtc gtc tgc tgc tcg atg tcc tac aca tgg   6649
Glu Glu Ala Ser Glu Asp Val Val Cys Cys Ser Met Ser Tyr Thr Trp
                1605                1610                1615

aca ggc gcc ctg atc acg cca tgc gct gcg gag gaa acc aag ctg ccc   6697
Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu Pro
            1620                1625                1630

atc aat gca ctg agc aac tct ttg ctc cgt cac cac aac ttg gtc tat   6745
Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr
        1635                1640                1645

gct aca aca tct cgc agc gca agc ctg cgg cag aag aag gtc acc ttt   6793
Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr Phe
    1650                1655                1660

gac aga ctg cag gtc ctg gac gac cac tac cgg gac gtg ctc aag gag   6841
Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys Glu
1665                1670                1675                1680

atg aag gcg aag gcg tcc aca gtt aag gct aaa ctt cta tcc gtg gag   6889
Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val Glu
                1685                1690                1695

gaa gcc tgt aag ctg acg ccc cca cat tcg gcc aga tct aaa ttt ggc   6937
Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe Gly
            1700                1705                1710

tat ggg gca aag gac gtc cgg aac cta tcc agc aag gcc gtt aac cac   6985
Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
        1715                1720                1725

atc cgc tcc gtg tgg aag gac ttg ctg gaa gac act gag aca cca att   7033
Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro Ile
    1730                1735                1740

gac acc acc atc atg gca aaa aat gag gtt ttc tgc gtc caa cca gag   7081
Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu
1745                1750                1755                1760

aag ggg ggc cgc aag cca gct cgc ctt atc gta ttc cca gat ttg ggg   7129
Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly
                1765                1770                1775
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gtt cgt gtg tgc gag aaa atg gcc ctt tac gat gtg gtc tcc acc ctc   7177
Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr Leu
            1780                1785                1790

cct cag gcc gtg atg ggc tct tca tac gga ttc caa tac tct cct gga   7225
Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly
        1795                1800                1805

cag cgg gtc gag ttc ctg gtg aat gcc tgg aaa gcg aag aaa tgc cct   7273
Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys Pro
    1810                1815                1820

atg ggc ttc gca tat gac acc cgc tgt ttt gac tca acg gtc act gag   7321
Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
1825                1830                1835                1840

aat gac atc cgt gtt gag gag tca atc tac caa tgt tgt gac ttg gcc   7369
Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu Ala
                1845                1850                1855

ccc gaa gcc aga cag gcc ata agg tcg ctc aca gag cgg ctt tac atc   7417
Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr Ile
            1860                1865                1870

ggg ggc ccc ctg act aat tct aaa ggg cag aac tgc ggc tat cgc cgg   7465
Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg Arg
        1875                1880                1885

tgc cgc gcg agc ggt gta ctg acg acc agc tgc ggt aat acc ctc aca   7513
Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr
    1890                1895                1900

tgt tac ttg aag gcc gct gcg gcc tgt cga gct gcg aag ctc cag gac   7561
Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln Asp
1905                1910                1915                1920

tgc acg atg ctc gta tgc gga gac gac ctt gtc gtt atc tgt gaa agc   7609
Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser
                1925                1930                1935

gcg ggg acc caa gag gac gag gcg agc cta cgg gcc ttc acg gag gct   7657
Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu Ala
            1940                1945                1950

atg act aga tac tct gcc ccc cct ggg gac ccg ccc aaa cca gaa tac   7705
Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu Tyr
        1955                1960                1965

gac ttg gag ttg ata aca tca tgc tcc tcc aat gtg tca gtc gcg cac   7753
Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His
    1970                1975                1980

gat gca tct ggc aaa agg gtg tac tat ctc acc cgt gac ccc acc acc   7801
Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
1985                1990                1995                2000
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ccc ctt gcg cgg gct gcg tgg gag aca gct aga cac act cca gtc aat   7849
Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn
                2005                2010                2015

tcc tgg cta ggc aac atc atc atg tat gcg ccc acc ttg tgg gca agg   7897
Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg
            2020                2025                2030

atg atc ctg atg act cat ttc ttc tcc atc ctt cta gct cag gaa caa   7945
Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln
        2035                2040                2045

ctt gaa aaa gcc cta gat tgt cag atc tac ggg gcc tgt tac tcc att   7993
Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile
    2050                2055                2060

gag cca ctt gac cta cct cag atc att caa cga ctc cac ggc ctt agc   8041
Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu Ser
2065                2070                2075                2080

gca ttt tca ctc cat agt tac tct cca ggt gag atc aat agg gtg gct   8089
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
                2085                2090                2095

tca tgc ctc agg aaa ctt ggg gta ccg ccc ttg cga gtc tgg aga cat   8137
Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg His
            2100                2105                2110

cgg gcc aga agt gtc cgc gct agg cta ctg tcc cag ggg ggg agg gct   8185
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg Ala
        2115                2120                2125

gcc act tgt ggc aag tac ctc ttc aac tgg gca gta agg acc aag ctc   8233
Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
    2130                2135                2140

aaa ctc act cca atc ccg gct gcg tcc cag ttg gat tta tcc agc tgg   8281
Lys Leu Thr Pro Ile Pro Ala Ala Ser Gln Leu Asp Leu Ser Ser Trp
2145                2150                2155                2160

ttc gtt gct ggt tac agc ggg gga gac ata tat cac agc ctg tct cgt   8329
Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser Arg
                2165                2170                2175

gcc cga ccc cgc tgg ttc atg tgg tgc cta ctc cta ctt tct gta ggg   8377
Ala Arg Pro Arg Trp Phe Met Trp Cys Leu Leu Leu Leu Ser Val Gly
            2180                2185                2190

gta ggc atc tat cta ctc ccc aac cga tga acggggagct aaacactcca     8427
Val Gly Ile Tyr Leu Leu Pro Asn Arg  *
        2195                2200

ggccaatagg ccatcctgtt tttttccctt ttttttttte ttttttttte ttttttttte 8487
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c atg gac cgg gag atg gca gca tcg tgc gga ggc gcg gtt ttc gta ggt 1849

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Met Asp Arg Glu Met Ala Ala Ser Cys Gly Gly Ala Val Phe Val Gly
 1               5                  10                  15

ctg ata ctc ttg acc ttg tca ccg cac tat aag ctg ttc ctc gct agg   1897
Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala Arg
            20                  25                  30

ctc ata tgg tgg tta caa tat ttt atc acc agg gcc gag gca cac ttg   1945
Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His Leu
        35                  40                  45

caa gtg tgg atc ccc ccc ctc aac gtt cgg ggg ggc cgc gat gcc gtc   1993
Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
    50                  55                  60

atc ctc ctc acg tgc gcg atc cac cca gag cta atc ttt acc atc acc   2041
Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile Thr
65                  70                  75                  80

aaa atc ttg ctc gcc ata ctc ggt cca ctc atg gtg ctc cag gct ggt   2089
Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly
                85                  90                  95

ata acc aaa gtg ccg tac ttc gtg cgc gca cac ggg ctc att cgt gca   2137
Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg Ala
            100                 105                 110

tgc atg ctg gtg cgg aag gtt gct ggg ggt cat tat gtc caa atg gct   2185
Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala
        115                 120                 125

ctc atg aag ttg gcc gca ctg aca ggt acg tac gtt tat gac cat ctc   2233
Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His Leu
    130                 135                 140

acc cca ctg cgg gac tgg gcc cac gcg ggc cta cga gac ctt gcg gtg   2281
Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala Val
145                 150                 155                 160

gca gtt gag ccc gtc gtc ttc tct gat atg gag acc aag gtt atc acc   2329
Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile Thr
                165                 170                 175

tgg ggg gca gac acc gcg gcg tgt ggg gac atc atc ttg ggc ctg ccc   2377
Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
            180                 185                 190

gtc tcc gcc cgc agg ggg agg gag ata cat ctg gga ccg gca gac agc   2425
Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp Ser
        195                 200                 205

ctt gaa ggg cag ggg tgg cga ctc ctc gcg cct att acg gcc tac tcc   2473
Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser
    210                 215                 220

caa cag acg cga ggc cta ctt ggc tgc atc atc act agc ctc aca ggc   2521
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
225                 230                 235                 240
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cgg gac agg aac cag gtc gag ggg gag gtc caa gtg gtc tcc acc gca   2569
Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
                245                 250                 255

aca caa tct ttc ctg gcg acc tgc gtc aat ggc gtg tgt tgg act gtc   2617
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
            260                 265                 270

tat cat ggt gcc ggc tca aag acc ctt gcc ggc cca aag ggc cca atc   2665
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
        275                 280                 285

acc caa atg tac acc aat gtg gac cag gac ctc gtc ggc tgg caa gcg   2713
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
    290                 295                 300

ccc ccc ggg gcg cgt tcc ttg aca cca tgc acc tgc ggc agc tcg gac   2761
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
305                 310                 315                 320

ctt tac ttg gtc acg agg cat gcc gat gtc att ccg gtg cgc cgg cgg   2809
Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg
                325                 330                 335

ggc gac agc agg ggg agc cta ctc tcc ccc agg ccc gtc tcc tac ttg   2857
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
            340                 345                 350

aag ggc tct tcg ggc ggt cca ctg ctc tgc ccc tcg ggg cac gct gtg   2905
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
        355                 360                 365

ggc atc ttt cgg gct gcc gtg tgc acc cga ggg gtt gcg aag gcg gtg   2953
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
    370                 375                 380

gac ttt gta ccc gtc gag tct atg gaa acc act atg cgg tcc ccg gtc   3001
Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val
385                 390                 395                 400

ttc acg gac aac tcg tcc cct ccg gcc gta ccg cag aca ttc cag gtg   3049
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln Val
                405                 410                 415

gcc cat cta cac gcc cct act ggt agc ggc aag agc act aag gtg ccg   3097
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
            420                 425                 430

gct gcg tat gca gcc caa ggg tat aag gtg ctt gtc ctg aac ccg tcc   3145
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
        435                 440                 445

gtc gcc gcc acc cta ggt ttc ggg gcg tat atg tct aag gca cat ggt   3193
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
    450                 455                 460
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atc gac cct aac atc aga acc ggg gta agg acc atc acc acg ggt gcc   3241
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
465                 470                 475                 480

ccc atc acg tac tcc acc tat ggc aag ttt ctt gcc gac ggt ggt tgc   3289
Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
                485                 490                 495

tct ggg ggc gcc tat gac atc ata ata tgt gat gag tgc cac tca act   3337
Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
            500                 505                 510

gac tcg acc act atc ctg ggc atc ggc aca gtc ctg gac caa gcg gag   3385
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
        515                 520                 525

acg gct gga gcg cga ctc gtc gtg ctc gcc acc gct acg cct ccg gga   3433
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
    530                 535                 540

tcg gtc acc gtg cca cat cca aac atc gag gag gtg gct ctg tcc agc   3481
Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Ser
545                 550                 555                 560

act gga gaa atc ccc ttt tat ggc aaa gcc atc ccc atc gag acc atc   3529
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Thr Ile
                565                 570                 575

aag ggg ggg agg cac ctc att ttc tgc cat tcc aag aag aaa tgt gat   3577
Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp
            580                 585                 590

gag ctc gcc gcg aag ctg tcc ggc ctc gga ctc aat gct gta gca tat   3625
Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Leu Asn Ala Val Ala Tyr
        595                 600                 605

tac cgg ggc ctt gat gta tcc gtc ata cca act agc gga gac gtc att   3673
Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Ile
    610                 615                 620

gtc gta gca acg gac gct cta atg acg ggc ttt acc ggc gat ttc gac   3721
Val Val Ala Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp
625                 630                 635                 640

tca gtg atc gac tgc aat aca tgt gtc acc cag aca gtc gac ttc agc   3769
Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser
                645                 650                 655

ctg gac ccg acc ttc acc att gag acg acg acc gtg cca caa gac gcg   3817
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
            660                 665                 670

gtg tca cgc tcg cag cgg cga ggc agg act ggt agg ggc agg atg ggc   3865
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met Gly
        675                 680                 685
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att tac agg ttt gtg act cca gga gaa cgg ccc tcg ggc atg ttc gat   3913
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
    690                 695                 700

tcc tcg gtt ctg tgc gag tgc tat gac gcg ggc tgt gct tgg tac gag   3961
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
705                 710                 715                 720

ctc acg ccc gcc gag acc tca gtt agg ttg cgg gct tac cta aac aca   4009
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
                725                 730                 735

cca ggg ttg ccc gtc tgc cag gac cat ctg gag ttc tgg gag agc gtc   4057
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val
            740                 745                 750

ttt aca ggc ctc acc cac ata gac gcc cat ttc ttg tcc cag act aag   4105
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
        755                 760                 765

cag gca gga gac aac ttc ccc tac ctg gta gca tac cag gct acg gtg   4153
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
    770                 775                 780

tgc gcc agg gct cag gct cca cct cca tcg tgg gac caa atg tgg aag   4201
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
785                 790                 795                 800

tgt ctc ata cgg cta aag cct acg ctg cac ggg cca acg ccc ctg ctg   4249
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
                805                 810                 815

tat agg ctg gga gcc gtt caa aac gag gtt act acc aca cac ccc ata   4297
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro Ile
            820                 825                 830

acc aaa tac atc atg gca tgc atg tcg gct gac ctg gag gtc gtc acg   4345
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr
        835                 840                 845

agc acc tgg gtg ctg gta ggc gga gtc cta gca gct ctg gcc gcg tat   4393
Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
    850                 855                 860

tgc ctg aca aca ggc agc gtg gtc att gtg ggc agg atc atc ttg tcc   4441
Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
865                 870                 875                 880

gga aag ccg gcc atc att ccc gac agg gaa gtc ctt tac cgg gag ttc   4489
Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe
                885                 890                 895

gat gag atg gaa gag tgc gcc tca cac ctc cct tac atc gaa cag gga   4537
Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln Gly
            900                 905                 910
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atg cag ctc gcc gaa caa ttc aaa cag aag gca atc ggg ttg ctg caa   4585
Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu Gln
        915                 920                 925

aca gcc acc aag caa gcg gag gct gct gct ccc gtg gtg gaa tcc aag   4633
Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys
    930                 935                 940

tgg cgg acc ctc gaa gcc ttc tgg gcg aag cat atg tgg aat ttc atc   4681
Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe Ile
945                 950                 955                 960

agc ggg ata caa tat tta gca ggc ttg tcc act ctg cct ggc aac ccc   4729
Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro
                965                 970                 975

gcg ata gca tca ctg atg gca ttc aca gcc tct atc acc agc ccg ctc   4777
Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu
            980                 985                 990

acc acc caa cat acc ctc ctg ttt aac atc ctg ggg gga tgg gtg gcc   4825
Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala
        995                 1000                1005

gcc caa ctt gct cct ccc agc gct gct tct gct ttc gta ggc gcc ggc   4873
Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly
    1010                1015                1020

atc gct gga gcg gct gtt ggc agc ata ggc ctt ggg aag gtg ctt gtg   4921
Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val
1025                1030                1035                1040

gat att ttg gca ggt tat gga gca ggg gtg gca ggc gcg ctc gtg gcc   4969
Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala
                1045                1050                1055

ttt aag gtc atg agc ggc gag atg ccc tcc acc gag gac ctg gtt aac   5017
Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn
            1060                1065                1070

cta ctc cct gct atc ctc tcc cct ggc gcc cta gtc gtc ggg gtc gtg   5065
Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val
        1075                1080                1085

tgc gca gcg ata ctg cgt cgg cac gtg ggc cca ggg gag ggg gct gtg   5113
Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val
    1090                1095                1100

cag tgg atg aac cgg ctg ata gcg ttc gct tcg cgg ggt aac cac gtc   5161
Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val
1105                1110                1115                1120

tcc ccc acg cac tat gtg cct gag agc gac gct gca gca cgt gtc act   5209
Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr
                1125                1130                1135
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cag atc ctc tct agt ctt acc atc act cag ctg ctg aag agg ctt cac   5257
Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His
            1140                1145                1150

cag tgg atc aac gag gac tgc tcc acg cca tgc tcc ggc tcg tgg cta   5305
Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu
        1155                1160                1165

aga gat gtt tgg gat tgg ata tgc acg gtg ttg act gat ttc aag acc   5353
Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys Thr
    1170                1175                1180

tgg ctc cag tcc aag ctc ctg ccg cga ttg ccg gga gtc ccc ttc ttc   5401
Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe Phe
1185                1190                1195                1200

tca tgt caa cgt ggg tac aag gga gtc tgg cgg ggc gac ggc atc atg   5449
Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met
                1205                1210                1215

caa acc acc tgc cca tgt gga gca cag atc acc gga cat gtg aaa aac   5497
Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn
            1220                1225                1230

ggt tcc atg agg atc gtg ggg cct agg acc tgt agt aac acg tgg cat   5545
Gly Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp His
        1235                1240                1245

gga aca ttc ccc att aac gcg tac acc acg ggc ccc tgc acg ccc tcc   5593
Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser
    1250                1255                1260

ccg gcg cca aat tat tct agg gcg ctg tgg cgg gtg gct gct gag gag   5641
Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu
1265                1270                1275                1280

tac gtg gag gtt acg cgg gtg ggg gat ttc cac tac gtg acg ggc atg   5689
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met
                1285                1290                1295

acc act gac aac gta aag tgc ccg tgt cag gtt ccg gcc ccc gaa ttc   5737
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe
            1300                1305                1310

ttc aca gaa gtg gat ggg gtg cgg ttg cac agg tac gct cca gcg tgc   5785
Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys
        1315                1320                1325

aaa ccc ctc cta cgg gag gag gtc aca ttc ctg gtc ggg ctc aat caa   5833
Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn Gln
    1330                1335                1340

tac ctg gtt ggg tca cag ctc cca tgc gag ccc gaa ccg gac gta gca   5881
Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala
1345                1350                1355                1360
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gtg ctc act tcc atg ctc acc gac ccc tcc cac att acg gcg gag acg   5929
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr
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gct aag cgt agg ctg gcc agg gga tct ccc ccc tcc ttg gcc agc tca   5977
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser
            1380                1385                1390

tca gct agc cag ctg tct gcg cct tcc ttg aag gca aca tgc act acc   6025
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr
        1395                1400                1405

cgt cat gac tcc ccg gac gct gac ctc atc gag gcc aac ctc ctg tgg   6073
Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp
    1410                1415                1420

cgg cag gag atg ggc ggg aac atc acc cgc gtg gag tca gaa aat aag   6121
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys
1425                1430                1435                1440

gta gta att ttg gac tct ttc gag ccg ctc caa gcg gag gag gat gag   6169
Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp Glu
                1445                1450                1455

agg gaa gta tcc gtt ccg gcg gag atc ctg cgg agg tcc agg aaa ttc   6217
Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys Phe
            1460                1465                1470

cct cga gcg atg ccc ata tgg gca cgc ccg gat tac aac cct cca ctg   6265
Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu
        1475                1480                1485

tta gag tcc tgg aag gac ccg gac tac gtc cct cca gtg gta cac ggg   6313
Leu Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His Gly
    1490                1495                1500

tgt cca ttg ccg cct gcc aag gcc cct ccg ata cca cct cca cgg agg   6361
Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg Arg
1505                1510                1515                1520

aag agg acg gtt gtc ctg tca gaa tct acc gtg tct tct gcc ttg gcg   6409
Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu Ala
                1525                1530                1535

gag ctc gcc aca aag acc ttc ggc agc tcc gaa tcg tcg gcc gtc gac   6457
Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val Asp
            1540                1545                1550

agc ggc acg gca acg gcc tct cct gac cag ccc tcc gac gac ggc gac   6505
Ser Gly Thr Ala Thr Ala Ser Pro Asp Gln Pro Ser Asp Asp Gly Asp
        1555                1560                1565

gcg gga tcc gac gtt gag tcg tac tcc tcc atg ccc ccc ctt gag ggg   6553
Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly
    1570                1575                1580
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gag ccg ggg gat ccc gat ctc agc gac ggg tct tgg tct acc gta agc   6601
Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser
1585                1590                1595                1600

gag gag gct agt gag gac gtc gtc tgc tgc tcg atg tcc tac aca tgg   6649
Glu Glu Ala Ser Glu Asp Val Val Cys Cys Ser Met Ser Tyr Thr Trp
                1605                1610                1615

aca ggc gcc ctg atc acg cca tgc gct gcg gag gaa acc aag ctg ccc   6697
Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu Pro
            1620                1625                1630

atc aat gca ctg agc aac tct ttg ctc cgt cac cac aac ttg gtc tat   6745
Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr
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gct aca aca tct cgc agc gca agc ctg cgg cag aag aag gtc acc ttt   6793
Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr Phe
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gac aga ctg cag gtc ctg gac gac cac tac cgg gac gtg ctc aag gag   6841
Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys Glu
1665                1670                1675                1680

atg aag gcg aag gcg tcc aca gtt aag gct aaa ctt cta tcc gtg gag   6889
Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val Glu
                1685                1690                1695

gaa gcc tgt aag ctg acg ccc cca cat tcg gcc aga tct aaa ttt ggc   6937
Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe Gly
            1700                1705                1710

tat ggg gca aag gac gtc cgg aac cta tcc agc aag gcc gtt aac cac   6985
Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
        1715                1720                1725

atc cgc tcc gtg tgg aag gac ttg ctg gaa gac act gag aca cca att   7033
Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro Ile
    1730                1735                1740

gac acc acc atc atg gca aaa aat gag gtt ttc tgc gtc caa cca gag   7081
Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu
1745                1750                1755                1760

aag ggg ggc cgc aag cca gct cgc ctt atc gta ttc cca gat ttg ggg   7129
Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly
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gtt cgt gtg tgc gag aaa atg gcc ctt tac gat gtg gtc tcc acc ctc   7177
Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr Leu
            1780                1785                1790

cct cag gcc gtg atg ggc tct tca tac gga ttc caa tac tct cct gga   7225
Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly
        1795                1800                1805
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cag cgg gtc gag ttc ctg gtg aat gcc tgg aaa gcg aag aaa tgc cct   7273
Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys Pro
    1810                1815                1820

atg ggc ttc gca tat gac acc cgc tgt ttt gac tca acg gtc act gag   7321
Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
1825                1830                1835                1840

aat gac atc cgt gtt gag gag tca atc tac caa tgt tgt gac ttg gcc   7369
Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu Ala
                1845                1850                1855

ccc gaa gcc aga cag gcc ata agg tcg ctc aca gag cgg ctt tac atc   7417
Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr Ile
            1860                1865                1870

ggg ggc ccc ctg act aat tct aaa ggg cag aac tgc ggc tat cgc cgg   7465
Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg Arg
        1875                1880                1885

tgc cgc gcg agc ggt gta ctg acg acc agc tgc ggt aat acc ctc aca   7513
Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr
    1890                1895                1900

tgt tac ttg aag gcc gct gcg gcc tgt cga gct gcg aag ctc cag gac   7561
Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln Asp
1905                1910                1915                1920

tgc acg atg ctc gta tgc gga gac gac ctt gtc gtt atc tgt gaa agc   7609
Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser
                1925                1930                1935

gcg ggg acc caa gag gac gag gcg agc cta cgg gcc ttc acg gag gct   7657
Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu Ala
            1940                1945                1950

atg act aga tac tct gcc ccc cct ggg gac ccg ccc aaa cca gaa tac   7705
Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu Tyr
        1955                1960                1965

gac ttg gag ttg ata aca tca tgc tcc tcc aat gtg tca gtc gcg cac   7753
Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His
    1970                1975                1980

gat gca tct ggc aaa agg gtg tac tat ctc acc cgt gac ccc acc acc   7801
Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
1985                1990                1995                2000

ccc ctt gcg cgg gct gcg tgg gag aca gct aga cac act cca gtc aat   7849
Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn
                2005                2010                2015

tcc tgg cta ggc aac atc atc atg tat gcg ccc acc ttg tgg gca agg   7897
Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg
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Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln
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ctt gaa aaa gcc cta gat tgt cag atc tac ggg gcc tgt tac tcc att   7993
Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile
    2050                2055                2060

gag cca ctt gac cta cct cag atc att caa cga ctc cac ggc ctt agc   8041
Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu Ser
2065                2070                2075                2080

gca ttt tca ctc cat agt tac tct cca ggt gag atc aat agg gtg gct   8089
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
                2085                2090                2095

tca tgc ctc agg aaa ctt ggg gta ccg ccc ttg cga gtc tgg aga cat   8137
Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg His
            2100                2105                2110

cgg gcc aga agt gtc cgc gct agg cta ctg tcc cag ggg ggg agg gct   8185
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg Ala
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gcc act tgt ggc aag tac ctc ttc aac tgg gca gta agg acc aag ctc   8233
Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
    2130                2135                2140

aaa ctc act cca atc ccg gct gcg tcc cag ttg gat tta tcc agc tgg   8281
Lys Leu Thr Pro Ile Pro Ala Ala Ser Gln Leu Asp Leu Ser Ser Trp
2145                2150                2155                2160

ttc gtt gct ggt tac agc ggg gga gac ata tat cac agc ctg tct cgt   8329
Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser Arg
                2165                2170                2175

gcc cga ccc cgc tgg ttc atg tgg tgc cta ctc cta ctt tct gta ggg   8377
Ala Arg Pro Arg Trp Phe Met Trp Cys Leu Leu Leu Leu Ser Val Gly
            2180                2185                2190

gta ggc atc tat cta ctc ccc aac cga tga acggggagct aaacactcca     8427
Val Gly Ile Tyr Leu Leu Pro Asn Arg  *
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Leu Ile Leu Leu Thr Leu Ser Pro His Tyr Lys Leu Phe Leu Ala Arg
            20   25   30

ctc ata tgg tgg tta caa tat ttt atc acc agg gcc gag gca cac ttg 1945
Leu Ile Trp Trp Leu Gln Tyr Phe Ile Thr Arg Ala Glu Ala His Leu
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caa gtg tgg atc ccc ccc ctc aac gtt cgg ggg ggc cgc gat gcc gtc 1993
Gln Val Trp Ile Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val
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atc ctc ctc acg tgc gcg atc cac cca gag cta atc ttt acc atc acc 2041
Ile Leu Leu Thr Cys Ala Ile His Pro Glu Leu Ile Phe Thr Ile Thr
65   70   75   80

aaa atc ttg ctc gcc ata ctc ggt cca ctc atg gtg ctc cag gct ggt 2089
Lys Ile Leu Leu Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly
                85   90   95

ata acc aaa gtg ccg tac ttc gtg cgc gca cac ggg ctc att cgt gca 2137
Ile Thr Lys Val Pro Tyr Phe Val Arg Ala His Gly Leu Ile Arg Ala
            100   105   110

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Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala
        115                 120                 125

ctc atg aag ttg gcc gca ctg aca ggt acg tac gtt tat gac cat ctc   2233
Leu Met Lys Leu Ala Ala Leu Thr Gly Thr Tyr Val Tyr Asp His Leu
    130                 135                 140

acc cca ctg cgg gac tgg gcc cac gcg ggc cta cga gac ctt gcg gtg   2281
Thr Pro Leu Arg Asp Trp Ala His Ala Gly Leu Arg Asp Leu Ala Val
145                 150                 155                 160

gca gtt gag ccc gtc gtc ttc tct gat atg gag acc aag gtt atc acc   2329
Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Val Ile Thr
                165                 170                 175

tgg ggg gca gac acc gcg gcg tgt ggg gac atc atc ttg ggc ctg ccc   2377
Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
            180                 185                 190

gtc tcc gcc cgc agg ggg agg gag ata cat ctg gga ccg gca gac agc   2425
Val Ser Ala Arg Arg Gly Arg Glu Ile His Leu Gly Pro Ala Asp Ser
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ctt gaa ggg cag ggg tgg cga ctc ctc gcg cct att acg gcc tac tcc   2473
Leu Glu Gly Gln Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser
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caa cag acg cga ggc cta ctt ggc tgc atc atc acc agc ctc aca ggc   2521
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
225                 230                 235                 240

cgg gac agg aac cag gtc gag ggg gag gtc caa gtg gtc tcc acc gca   2569
Arg Asp Arg Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
                245                 250                 255

aca caa tct ttc ctg gcg acc tgc gtc aat ggc gtg tgt tgg act gtc   2617
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
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tat cat ggt gcc ggc tca aag acc ctt gcc ggc cca aag ggc cca atc   2665
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
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acc caa atg tac acc aat gtg gac cag gac ctc gtc ggc tgg caa gcg   2713
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Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
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Leu Tyr Leu Val Thr Lys His Ala Asp Val Ile Pro Val Arg Arg Arg
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ggc gac agc agg ggg agc cta ctc tcc ccc cgg ccc gtc tcc tac ttg   2857
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
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aag ggc tct tcg ggc ggt cca ctg ctc tgc ccc tcg ggg cac gct gtg   2905
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
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ggc atc ttt cgg gct gcc gtg tgc acc cga ggg gtt gcg aag gcg gtg   2953
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
    370                 375                 380

gac ttt gta ccc gtc gag tct atg gaa acc act atg cgg tcc ccg gtc   3001
Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val
385                 390                 395                 400

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Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Thr Phe Gln Val
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gcc cat cta cac gcc cct act ggt agc ggc aag agc act aag gtg ccg   3097
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
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gct gcg tat gca gcc caa ggg tat aag gtg ctt gtc ctg aac ccg tcc   3145
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
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gtc gcc gcc acc cta ggt ttc ggg gcg tat atg tct aag gca cat ggt   3193
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
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atc gac cct aac atc aga acc ggg gta agg acc atc acc acg ggt gcc   3241
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
465                 470                 475                 480

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Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
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Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
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Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
        515                 520                 525

acg gct gga gcg cga ctc gtc gtg ctc gcc acc gct acg cct ccg gga   3433
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
    530                 535                 540

tcg gtc acc gtg cca cat cca aac atc gag gag gtg gct ctg tcc agc   3481
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545                 550                 555                 560
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Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
660 665 670

gtg tca cgc tcg cag cgg cga ggc agg act ggt agg ggc agg atg ggc 3865
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Met Gly
675 680 685

att tac agg ttt gtg act cca gga gaa cgg ccc tcg ggc atg ttc gat 3913
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
690 695 700

tcc tcg gtt ctg tgc gag tgc tat gac gcg ggc tgt gct tgg tac gag 3961
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
705 710 715 720

ctc acg ccc gcc gag acc tca gtt agg ttg cgg gct tac cta aac aca 4009
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
725 730 735

cca ggg ttg ccc gtc tgc cag gac cat ctg gag ttc tgg gag ggc gtc 4057
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly Val
740 745 750

ttt aca ggc ctc acc cac ata gac gcc cat ttc ttg tcc cag act aag 4105
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
755 760 765

cag gca gga gac aac ttc ccc tac ctg gta gca tac cag gct acg gtg 4153
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
770 775 780

tgc gcc agg gct cag gct cca cct cca tcg tgg gac caa atg tgg aag 4201
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
785 790 795 800

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tgt ctc ata cgg cta aag cct acg ctg cac ggg cca acg ccc ctg ctg   4249
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
                805                 810                 815

tat agg ctg gga gcc gtt caa aac gag gtt act acc aca cac ccc ata   4297
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Thr Thr His Pro Ile
            820                 825                 830

acc aaa tac atc atg gca tgc atg tcg gct gac ctg gag gtc gtc acg   4345
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr
        835                 840                 845

agc acc tgg gtg ctg gta ggc gga gtc cta gca gct ctg gct gcg tat   4393
Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
    850                 855                 860

tgc ctg aca aca ggc agc gtg gtc att gtg ggc agg atc atc ttg tcc   4441
Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
865                 870                 875                 880

gga agg ccg gcc atc att ccc gac agg gaa gtc ctt tac cgg gag ttc   4489
Gly Arg Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu Phe
                885                 890                 895

gat gag atg gaa gag tgt gcc tca cac ctc cct tac atc gaa cag gga   4537
Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gln Gly
            900                 905                 910

atg cag ctc gcc gaa caa ttc aaa cag aag gca atc ggg ttg ctg caa   4585
Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Ile Gly Leu Leu Gln
        915                 920                 925

aca gcc acc aag caa gcg gag gct gct gct ccc gtg gtg gaa tcc aag   4633
Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys
    930                 935                 940

tgg cgg acc ctc gaa gcc ttc tgg gcg aag cat atg tgg aat ttc atc   4681
Trp Arg Thr Leu Glu Ala Phe Trp Ala Lys His Met Trp Asn Phe Ile
945                 950                 955                 960

agc ggg ata caa tat tta gca ggc ttg tcc act ctg cct ggc aac ccc   4729
Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro
                965                 970                 975

gcg ata gca tca ctg atg gca ttc aca gcc tct atc acc agc ccg ctc   4777
Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu
            980                 985                 990

acc acc caa cat acc ctc ctg ttt aac atc ctg ggg gga tgg gtg gcc   4825
Thr Thr Gln His Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala
        995                 1000                1005

gcc caa ctt gct cct ccc agc gct gct tcc gct ttc gta ggc gcc ggc   4873
Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly
    1010                1015                1020
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atc gct gga gcg gct gtt ggc agc ata ggc ctt ggg aag gtg ctt gtg   4921
Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val
1025                1030                1035                1040

gat att ttg gca ggt tat gga gca ggg gtg gca ggc gcg ctc gtg gcc   4969
Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala
                1045                1050                1055

ttt aag gtc atg agc ggc gag atg ccc tcc acc gag gac ctg gtt aac   5017
Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn
            1060                1065                1070

cta ctc cct gct atc ctc tcc cct ggc gcc cta gtc gtc ggg gtc gtg   5065
Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val
        1075                1080                1085

tgc gca gcg ata ctg cgt cgg cac gtg ggc cca ggg gag ggg gct gtg   5113
Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val
    1090                1095                1100

cag tgg atg aac cgg ctg ata gcg ttc gct tcg cgg ggt aac cac gtc   5161
Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val
1105                1110                1115                1120

tcc ccc acg cac tat gtg cct gag agc gac gct gca gca cgt gtc act   5209
Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr
                1125                1130                1135

cag atc ctc tct agt ctt acc atc act cag ctg ctg aag agg ctt cac   5257
Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His
            1140                1145                1150

cag tgg atc aac gag gac tgc tcc acg cca tgc tcc ggc tcg tgg cta   5305
Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu
        1155                1160                1165

aga gat gtt tgg gat tgg ata tgc acg gtg ttg act gat ttc aag gcc   5353
Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys Ala
    1170                1175                1180

tgg ctc cag tcc aag ctc ctg ccg cga ttg ccg gga gtc ccc ttc ttc   5401
Trp Leu Gln Ser Lys Leu Leu Pro Arg Leu Pro Gly Val Pro Phe Phe
1185                1190                1195                1200

tca tgt caa cgt ggg tac aag gga gtc tgg cgg ggc gac ggc atc atg   5449
Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met
                1205                1210                1215

caa acc acc tgc cca tgt gga gca cag atc acc gga cat gtg aaa aac   5497
Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn
            1220                1225                1230

tgt tcc atg agg atc gtg ggg cct agg acc tgt agt aac acg tgg cat   5545
Cys Ser Met Arg Ile Val Gly Pro Arg Thr Cys Ser Asn Thr Trp His
        1235                1240                1245
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gga aca ttc ccc att aac gcg tac acc acg ggc ccc tgc acg ccc tcc   5593
Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser
    1250                1255                1260

ccg gcg cca aat tat tct agg gcg ctg tgg cgg gtg gct gct gag gag   5641
Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu
1265                1270                1275                1280

tac gtg gag gtt acg cga gtg ggg gat ttc cac tac gtg acg ggc atg   5689
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met
                1285                1290                1295

acc act gac aac gta aag tgc ccg tgt cag gtt ccg gcc ccc gaa ttc   5737
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe
            1300                1305                1310

ttc aca gaa gtg gat ggg gtg cgg ttg cac agg tac gct cca gcg tgc   5785
Phe Thr Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys
        1315                1320                1325

aaa ccc ctc cta cgg gag gag gtc aca ttc ctg gtc ggg ctc aat caa   5833
Lys Pro Leu Leu Arg Glu Glu Val Thr Phe Leu Val Gly Leu Asn Gln
    1330                1335                1340

tac ccg gtt ggg tca cag ctc cca tgc gag ccc gaa ctg gac gta gca   5881
Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Leu Asp Val Ala
1345                1350                1355                1360

gtg ctc act tcc atg ctc acc gac ccc tcc cac att acg gcg gag acg   5929
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr
                1365                1370                1375

gct aag cgt agg ctg gcc agg gga tct ccc ccc tcc ttg gcc agc tca   5977
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser
            1380                1385                1390

tca gct agc cag ctg tct gcg cct tcc ttg aag gca aca tgc act acc   6025
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr
        1395                1400                1405

cgt cat gac tcc ccg gac gct gac ctc atc gag gcc aac ctc ctg tgg   6073
Arg His Asp Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp
    1410                1415                1420

cgg cag gag atg ggc ggg aac atc acc cgc gtg gag tca gag aat aag   6121
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys
1425                1430                1435                1440

gta gta att ttg gac tct ttc gag ccg ctc caa gcg gag gag gat gag   6169
Val Val Ile Leu Asp Ser Phe Glu Pro Leu Gln Ala Glu Glu Asp Glu
                1445                1450                1455

agg gaa gta tcc gtt ccg gcg gag atc ctg cgg agg tcc agg aaa ttc   6217
Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Arg Ser Arg Lys Phe
            1460                1465                1470
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cct cga gcg atg ccc ata tgg gca cgc ccg gat tac aac cct cca ctg   6265
Pro Arg Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu
        1475                1480                1485

tta gag tcc tgg aag gac ccg gac tac gtc cct cca gtg gta cac ggg   6313
Leu Glu Ser Trp Lys Asp Pro Asp Tyr Val Pro Pro Val Val His Gly
    1490                1495                1500

tgt cca ttg ccg cct gcc aag gcc cct ccg ata cca cct cca cgg agg   6361
Cys Pro Leu Pro Pro Ala Lys Ala Pro Pro Ile Pro Pro Pro Arg Arg
1505                1510                1515                1520

aag agg acg gtt gtc ctg tca gaa tct acc gtg tct tct gcc ttg gcg   6409
Lys Arg Thr Val Val Leu Ser Glu Ser Thr Val Ser Ser Ala Leu Ala
                1525                1530                1535

gag ctc gcc aca aag acc ttc ggc agc tcc gaa tcg tcg gcc gtc gac   6457
Glu Leu Ala Thr Lys Thr Phe Gly Ser Ser Glu Ser Ser Ala Val Asp
            1540                1545                1550

agc ggc acg gca acg gcc tct cct gac cag ccc tcc gac gac ggc gac   6505
Ser Gly Thr Ala Thr Ala Ser Pro Asp Gln Pro Ser Asp Asp Gly Asp
        1555                1560                1565

gcg gga tcc gac gtt gag tcg tac tcc tcc atg ccc ccc ctt gag ggg   6553
Ala Gly Ser Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly
    1570                1575                1580

gag ccg ggg gat ccc gat ctc agc gac ggg tct tgg tct acc gta agc   6601
Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser
1585                1590                1595                1600

gag gag gct agt gag gac gtc gtc tgc tgc tcg atg tcc tac aca tgg   6649
Glu Glu Ala Ser Glu Asp Val Val Cys Cys Ser Met Ser Tyr Thr Trp
                1605                1610                1615

aca ggc gcc ctg atc acg cca tgc gct gcg gag gaa acc aag ctg ccc   6697
Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala Glu Glu Thr Lys Leu Pro
            1620                1625                1630

atc aat gca ctg agc aac tct ttg ctc cgt cac cac aac ttg gtc tat   6745
Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr
        1635                1640                1645

gct aca aca tct cgc agc gca agc ctg cgg cag aag aag gtc acc ttt   6793
Ala Thr Thr Ser Arg Ser Ala Ser Leu Arg Gln Lys Lys Val Thr Phe
    1650                1655                1660

gac aga ctg cag gtc ctg gac gac cac tac cgg gac gtg ctc aag gag   6841
Asp Arg Leu Gln Val Leu Asp Asp His Tyr Arg Asp Val Leu Lys Glu
1665                1670                1675                1680

atg aag gcg aag gcg tcc aca gtt aag gct aaa ctt cta tcc gtg gag   6889
Met Lys Ala Lys Ala Ser Thr Val Lys Ala Lys Leu Leu Ser Val Glu
                1685                1690                1695
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gaa gcc tgt aag ctg acg ccc cca cat tcg gcc aga tct aaa ttt ggc   6937
Glu Ala Cys Lys Leu Thr Pro Pro His Ser Ala Arg Ser Lys Phe Gly
            1700                1705                1710

tat ggg gca aag gac gtc cgg aac cta tcc agc aag gcc gtt aac cac   6985
Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
        1715                1720                1725

atc cgc tcc gtg tgg aag gac ttg ctg gaa gac act gag aca cca att   7033
Ile Arg Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Glu Thr Pro Ile
    1730                1735                1740

gac acc acc atc atg gca aaa aat gag gtt ttc tgc gtc caa cca gag   7081
Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu
1745                1750                1755                1760

aag ggg ggc cgc aag cca gct cgc ctt atc gta ttc cca gat ttg ggg   7129
Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly
                1765                1770                1775

gtt cgt gtg tgc gag aaa atg gcc ctt tac gat gtg gtc tcc acc ctc   7177
Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr Leu
            1780                1785                1790

cct cag gcc gtg atg ggc tct tca tac gga ttc caa tac tct cct gga   7225
Pro Gln Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly
        1795                1800                1805

cag cgg gtc gag ttc ctg gtg aat gcc tgg aaa gcg aag aaa tgc cct   7273
Gln Arg Val Glu Phe Leu Val Asn Ala Trp Lys Ala Lys Lys Cys Pro
    1810                1815                1820

atg ggc ttc gca tat gac acc cgc tgt ttt gac tca acg gtc act gag   7321
Met Gly Phe Ala Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu
1825                1830                1835                1840

aat gac atc cgt gtt gag gag tca atc tac caa tgt tgt gac ttg gcc   7369
Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr Gln Cys Cys Asp Leu Ala
                1845                1850                1855

ccc gaa gcc aga cag gcc ata agg tcg ctc aca gag cgg ctt tac atc   7417
Pro Glu Ala Arg Gln Ala Ile Arg Ser Leu Thr Glu Arg Leu Tyr Ile
            1860                1865                1870

ggg ggc ccc ctg act aat tct aaa ggg cag aac tgc ggc tat cgc cgg   7465
Gly Gly Pro Leu Thr Asn Ser Lys Gly Gln Asn Cys Gly Tyr Arg Arg
        1875                1880                1885

tgc cgc gcg agc ggt gta ctg acg acc agc tgc ggt aat acc ctc aca   7513
Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr
    1890                1895                1900

tgt tac ttg aag gcc gct gcg gcc tgt cga gct gcg aag ctc cag gac   7561
Cys Tyr Leu Lys Ala Ala Ala Ala Cys Arg Ala Ala Lys Leu Gln Asp
1905                1910                1915                1920
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tgc acg atg ctc gta tgc gga gac gac ctt gtc gtt atc tgt gaa agc   7609
Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser
                1925                1930                1935

gcg ggg acc caa gag gac gag gcg agc cta cgg gcc ttc acg gag gct   7657
Ala Gly Thr Gln Glu Asp Glu Ala Ser Leu Arg Ala Phe Thr Glu Ala
            1940                1945                1950

atg act aga tac tct gcc ccc cct ggg gac ccg ccc aaa cca gaa tac   7705
Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Lys Pro Glu Tyr
        1955                1960                1965

gac ttg gag ttg ata aca tca tgc tcc tcc aat gtg tca gtc gcg cac   7753
Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His
    1970                1975                1980

gat gca tct ggc aaa agg gtg tac tat ctc acc cgt gac ccc acc acc   7801
Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr
1985                1990                1995                2000

ccc ctt gcg cgg gct gcg tgg gag aca gct aga cac act cca gtc aat   7849
Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn
                2005                2010                2015

tcc tgg cta ggc aac atc atc atg tat gcg ccc acc ttg tgg gca agg   7897
Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg
            2020                2025                2030

atg atc ctg atg act cat ttc ttc tcc atc ctt cta gct cag gaa caa   7945
Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln
        2035                2040                2045

ctt gaa aaa gcc cta gat tgt cag atc tac ggg gcc tgt tac tcc att   7993
Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile
    2050                2055                2060

gag cca ctt gac cta cct cag atc att caa cga ctc cac ggc ctt agc   8041
Glu Pro Leu Asp Leu Pro Gln Ile Ile Gln Arg Leu His Gly Leu Ser
2065                2070                2075                2080

gca ttt tca ctc cat agt tac tct cca ggt gag atc aat agg gtg gct   8089
Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala
                2085                2090                2095

tca tgc ctc agg aaa ctt ggg gta ccg ccc ttg cga gtc tgg aga cat   8137
Ser Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Val Trp Arg His
            2100                2105                2110

cgg gcc aga agt gtc cgc gct agg cta ctg tcc cag ggg ggg agg gct   8185
Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ser Gln Gly Gly Arg Ala
        2115                2120                2125

gcc act tgt ggc aag tac ctc ttc aac tgg gca gta agg acc aag ctc   8233
Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu
    2130                2135                2140
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aaa ctc act cca atc ccg gct gcg tcc cag ttg gat tta tcc agc tgg   8281
Lys Leu Thr Pro Ile Pro Ala Ala Ser Gln Leu Asp Leu Ser Ser Trp
2145                2150                2155                2160

ttc gtt gct ggt tac agc ggg gga gac ata tat cac agc ctg tct cgt   8329
Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser Arg
                2165                2170                2175

gcc cga ccc cgc tgg ttc atg tgg tgc cta ctc cta ctt tct gta ggg   8377
Ala Arg Pro Arg Trp Phe Met Trp Cys Leu Leu Leu Leu Ser Val Gly
            2180                2185                2190

gta ggc atc tat cta ctc ccc aac cga tga acggggagct aaacactcca     8427
Val Gly Ile Tyr Leu Leu Pro Asn Arg  *
        2195                2200

ggccaatagg ccatcctgtt tttttccctt ttttttttte ttttttttte ttttttttte 8487
ttttttttte ttttctcctt ttttttteet ctttttttee ttttctttee tttggtggct 8547
ccatcttagc cctagtcacg gctagctgtg aaaggtccgt gagccgcttg actgcagaga 8607
gtgctgatac tggcctctct gcagatcaag t                                8638
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(54) Title: SELF-REPLICATING RNA MOLECULE FROM HEPATITIS C VIRUS

(57) Abstract: A unique HCV RNA molecule is provided having an enhanced efficiency of establishing cell culture replication. Novel adaptive mutations have been identified within the HCV non-structural region that improves the efficiency of establishing persistently replicating HCV RNA in cell culture. This self-replicating polynucleotide molecule contains, contrary to all previous reports, a 5'-NTR that can be either an A as an alternative to the G already disclosed and therefore provides an alternative to existing systems comprising a self-replicating HCV RNA molecule. The G-->A mutation gives rise to HCV RNA molecules that, in conjunction with mutations in the HCV non-structural region, such as the G(2042)C/R mutations, possess greater efficiency of transduction and/or replication. These RNA molecules when transfected in a cell line are useful for evaluating potential inhibitors of HCV replication.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/01843

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/51 C12N15/40 C12Q1/68 C12Q1/70 C12N5/10
C12N7/04 C12N15/85

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, MEDLINE, SEQUENCE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LOHMANN V ET AL: "Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line." SCIENCE (WASHINGTON D C), vol. 285, no. 542, 2 July 1999 (1999-07-02), pages 110-113, XP002232924 ISSN: 0036-8075 the whole document ---	1-22
A	EP 1 043 399 A (BARTENSCHLAGER RALF DR) 11 October 2000 (2000-10-11) page 3 -page 24; tables 1,3 ---	1-22
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 2003	01 07 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schulz, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/01843

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BLIGHT K J ET AL: "EFFICIENT INITIATION OF HCV RNA REPLICATION IN CELL CULTURE" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 290, 8 December 2000 (2000-12-08), pages 1972-1974, XP002951271 ISSN: 0036-8075 page 1972 -page 1973; table 1 -----	1-22

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 01/01843

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-22

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-22

A hepatitis C (HCV) replicon comprising: a 5'-non translated region (NTR) wherein guanin at position 1 is substituted for adenine, a HCV polyprotein region coding for a HCV polyprotein further comprising one or more amino acid substitutions (adaptive mutations) in a non-structural protein and a 3'NTR; a eurkaryotic host cell transfected with said replicon; a RNA replication assay making use of said host cell and a method for testing compounds that inhibit HCV replication using said host cell.

2. Claims: 23-42 (in part)

A hepatitis C (HCV) replicon comprising: a 5'-non translated region (NTR), a HCV polyprotein region coding for a HCV polyprotein comprising a R(1135)K amino acid substitution (adaptive mutation) and a 3'NTR; a eurkaryotic host cell transfected with said replicon; a RNA replication assay making use of said host cell and a method for testing compounds that inhibit HCV replication using said host cell.

3. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a S(1148)G substitution.

4. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a S(1560)G substitution.

5. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a K(1691)R substitution.

6. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a L(1701)F substitution.

7. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a I(1984)V substitution.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

8. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a T(1993)A substitution.

9. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a G(2042)C or a G(2042)R substitution.

10. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a S(2404)P substitution.

11. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a L(2155)P substitution.

12. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a P(2166)L substitution.

13. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a M(2992)T substitution.

14. Claims: 23-42 (in part)

Idem as subject-matter 2 wherein the adaptive mutation is a E(1202)G substitution.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Inter[redacted]nal Application No
PCT/CA 01/01843

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1043399 A	11-10-2000	DE 19915178 A1	05-10-2000
		AT 236988 T	15-04-2003
		AU 2518000 A	19-10-2000
		CA 2303526 A1	03-10-2000
		DE 50001673 D1	15-05-2003
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